codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00100 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

ALINORM 06/29/31

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION

Twenty-ninth Session

Geneva, Switzerland, 3-7 July 2006

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

Cancun, Mexico, 8-12 May 2006

Note: *This report includes Codex Circular Letter CL 2006/14-RVDF*

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CX 4/60.2 **CL 2006/14-RVDF**
May 2006

TO: Codex Contact Points
Interested International Organizations

FROM: Secretary, Codex Alimentarius Commission,
Joint FAO/WHO Food Standards Programme
Viale delle Terme di Caracalla, 00100 Rome, Italy

SUBJECT: **Distribution of the Report of the Sixteenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods (ALINORM 06/29/31)**

The report of the Sixteenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods will be considered by the 29th Session of the Codex Alimentarius Commission (Geneva, Switzerland, 3–7 July 2006).

PART A - MATTERS FOR ADOPTION BY THE 29TH SESSION OF THE CODEX ALIMENTARIUS COMMISSION

DRAFT STANDARDS AND RELATED TEXTS AT STEP 8 OF THE UNIFORM PROCEDURE

1. **Draft Maximum Residue Limits, at Step 8** (para. 77 and Appendix II);
2. **Compendium of Methods of Analysis Identified as Suitable for Support to Codex MRLs, for adoption** (para. 77 and Appendix IX).

Governments and interested international organizations wishing to propose amendments or to comment on the above texts should do so in writing in conformity with the Uniform Procedure for the Elaboration of Codex Standards and Related Texts (at Step 8 or 5/8) (*Codex Alimentarius Commission Procedural Manual*, Fifteenth Edition) to the Secretary, Codex Alimentarius Commission, Viale delle Terme di Caracalla, 00100 Rome, Italy (telefax: +39.06.5705.4593; e-mail: codex@fao.org (***preferably***)) **no later than 31 May 2006.**

PROPOSED DRAFT STANDARDS AND RELATED TEXTS AT STEP 5 OF THE UNIFORM PROCEDURE

3. **Proposed Draft Maximum Residue Limits, at Step 5** (para. 77 and Appendix IV)**;**
4. **Proposed draft revised "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 5** (para. 86 and Appendix VII).

Governments and interested international organizations wishing to propose amendments or to comment on the above texts should do so in writing in conformity with the Uniform Procedure for the Elaboration of Codex Standards and Related Texts (at Step 5) (*Codex Alimentarius Commission Procedural Manual*, Fifteenth Edition) to the Secretary, Codex Alimentarius Commission, Viale delle Terme di Caracalla, 00100 Rome, Italy (telefax: +39.06.5705.4593; e-mail: codex@fao.org (***preferably***)) **no later than 31 May 2006.**

PART B - MATTERS FOR ADOPTION BY THE 30TH SESSION OF THE CODEX ALIMENTARIUS COMMISSION

5. Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and Risk Assessment Policy for the Setting of MRLs in Food, for adoption (para. 111 and Appendices VIII and IX)

Governments wishing to propose amendments or to comment regarding the implications which the above texts or any provisions thereof may have for their economic interests should do so in writing in conformity with the Uniform Procedure for the Elaboration of Codex Standards and Related Texts (at Step 5) (Codex Alimentarius Commission Procedural Manual, Fifteenth Edition) to the Secretary, Codex Alimentarius Commission, Viale delle Terme di Caracalla, 00100 Rome, Italy (telefax: +39.06.5705.4593; e-mail: codex@fao.org (***preferably***)) **no later than 1 December 2006.**

PART C – REQUEST FOR COMMENTS/INFORMATION

6. Proposed Draft Maximum Residue Limits, at Step 3 (para. 77 and Appendix VI)**;**

7. Information on registered use of Flumequine in Black tiger shrimp and in shrimps (para. 54)

Governments and interested international organizations wishing to comment on the above proposed draft MRLs should do so in writing in conformity with the Uniform Procedure for the Elaboration of Codex Standards and Related Texts (at Step 3) (*Codex Alimentarius Commission Procedural Manual*, Fifteenth Edition) to the Secretary, Codex Alimentarius Commission, Viale delle Terme di Caracalla, 00100 Rome, Italy (telefax: +39.06.5705.4593; e-mail: codex@fao.org (***preferably***)) **no later than 31 March 2007.**

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SUMMARY AND CONCLUSIONS

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

MATTERS FOR ADOPTION/CONSIDERATION BY THE 29TH SESSION OF THE CODEX ALIMENTARIUS COMMISSION:

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

The Committee agreed to forward:

- Draft MRLs for Trichlorfon, Pirlimycin, Cypermethrin and alpha-Cypermethrin, and Doramectin, for adoption at Step 8 (para. 77 and Appendix II).

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

The Committee agreed to forward:

- Proposed draft MRLs for Colistin and Ractopamine, for adoption at Step 5 (para. 77 and Appendix IV);
- Proposed 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 adoption at Step 5 (para. 86 and Appendix VII).

Proposal for New Work

The Committee agreed to forward:

- Priority List of Veterinary Drugs Requiring Evaluation of Re-evaluation by JECFA (para. 133 and Appendix XI).

Other Matters for Consideration by the 29th Session of the Codex Alimentarius Commission

The Committee agreed:

- To leave in place the temporary MRL for Tilmicosin in sheep's milk until JECFA had evaluated the data, in view of the strong commitment of the sponsor to make available radiolabelled residue depletion study in dairy cattle and of two residue depletion studies for further evaluation by JECFA (paras 42-43);
- To forward the Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs (para. 120 and Appendix X).

MATTERS FOR ADOPTION/CONSIDERATION BY THE 30TH SESSION OF THE CODEX ALIMENTARIUS COMMISSION:

The Committee agreed:

- To forward the Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and the Risk Assessment Policy for the Setting of MRLs in Food to the Codex Alimentarius Commission, through the Codex Committee on General Principles, for adoption and inclusion in the Codex Procedural Manual (para. 111 and Appendices VIII and IX).

MATTERS REFERRED TO CODEX COMMITTEES AND TASK FORCES:

Executive Committee (CCEXEC)

The Committee agreed:

- To retain the MRLs for Melegenstrol acetate at Step 7 for further consideration at its next Session, because consensus could not be reached on their advancement (para. 73);
- To inform the 58th Session of the Executive Committee that work on the proposed 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 would be completed by its next Session (para. 86).

MATTERS OF INTEREST TO THE CODEX ALIMENTARIUS COMMISSION AND/OR CODEX COMMITTEES AND TASK FORCES:

The Committee 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 requesting information on registered use of Flumequine with the understanding that, if this information is not provided, it will discontinue work on these MRLs at its next Session (para. 54 and Appendices III and V);
- To circulate the proposed draft MRLs for Erythromycin and Triclabendazole for comments at Step 3 (para. 77 and Appendix VI);
- To establish an electronic Working Group, led by France, to prepare a Discussion Paper to identify risk management topics and options to be considered at the next Session of the Committee (para. 113);
- To ask the Codex Secretariat to issue a Circular Letter requesting that members and observers review the list of methods; review and update any addresses of contact points for information; advise of any methods for which they are no longer able to provide information; and provide information on substances and matrices for which validated methods are still required (para. 119);
- To reconvene the *ad hoc* Working Group on Methods of Analysis and Sampling, under the co-Chairmanship of Canada and United Kingdom, prior to its next Session to continue work on the identification of suitable methods of analysis for residues of veterinary drugs in foods on the basis of information received in response to the Circular Letter (para. 121);
- To re-establish the physical Working Group on Residues of Veterinary Drugs without ADI/MRL led by the European Community to consider Annex III (Starting Point for a Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation by JECFA) of CX/RVDF 06/16/13. In particular, the Working Group will: i) give further consideration to the prioritization of compounds on the list and update the list; ii) consider management option for compounds to be evaluated by JECFA where a management decision is pending; and iii) provide guidance on practical analytical methods suitable for use by national regulatory authority for these compounds (para. 134);
- To reconvene the *ad hoc* Working Group on Priorities prior to its next Session, under the chairmanship of Australia, to consider proposals for compounds to be evaluated or re-evaluated by JECFA and the report of the physical Working Group on Compounds with no ADI/MRL (para. 135).

LIST OF ABBREVIATIONS USED IN THIS REPORT

ADI	Acceptable Daily Intake
AOAC	Association of Analytical Chemists
bw	body weight
CAC	Codex Alimentarius Commission
CAC/RCP	Codex Alimentarius Commission / Recommended Code of Practice
CAC/GL	Codex Alimentarius Commission / Guidelines
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
CI	Consumers International
CL	Circular Letter
CRD	Conference Room Document
EC	European Community
FAO	Food and Agriculture Organization of the United Nations
IAEA	International Atomic Energy Administration
IFAH	International Federation for Animal Health
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Science
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MRL	Maximum Residue Limit
MRLVD	Maximum Residue Limit for Veterinary Drug
OIE	World Organization for Animal Health
QA	Quality Assurance (systems)
RIVM	National Institute of Public Health and the Environment
TRS	Technical Report Series
TMDI	Theoretical Maximum Daily Intake
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 Sixteenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods was held on 8-12 May 2006 in Cancun (Mexico), at the kind invitation of the Governments of Mexico and the United States of America. The Session was chaired by Dr Stephen Sundlof, Director, Center for Veterinary Medicine, United States Food and Drug Administration and co-chaired by Dr Octavio Carranza de Mendoza, Director of Import, Export Services and Animal Certification, Secretaria de Agricultura, Ganaderia, Desarrollo, Rural, Pesca y Alimentacion de Mexico – Servicio Nacional de Sanidad e Inocuidad y Calidad Agroalimentaria (SAGARPA-SENASICA). The Session was attended by delegates from 39 Member countries and 1 Member organization and Observers from 5 international organizations. The list of participants is attached to this report as Appendix I.

OPENING OF THE SESSION

2. Dr F. Edward Scarbrough, Manager of the US Codex Office, United States Department of Agriculture, opened the Session. Mr. Norman Bellino, FAO Representative in Mexico and Dr. Octavio Carranza de Mendoza also addressed the Committee on behalf of FAO and of the Government of Mexico, respectively.

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

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

4. The Committee agreed to consider: i) the recommendation of 54th JECFA regarding the MRL for Tilmicosin in sheep's milk under Agenda Item 6; and ii) the document on "Activities of the Food and Environmental Protection Section of the Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture Related to the Work of the Codex Committee on Residues of Veterinary Drugs in Foods" under Agenda Item 4.

5. In order to expedite its work, the Committee agreed to establish two *ad hoc* Working Groups on: i) Agenda Item 7 "Proposed Draft Revised Guidelines for the Establishment of a Regulatory Program for the Control of Veterinary Drug Residues in Foods"[2] and ii) Agenda Item 9 "Risk Management Methodologies, including Risk Assessment Policies, in the Codex Committee on Residues of Veterinary Drugs in Foods"[3].

6. The Committee agreed to change the order of the discussion and to consider Agenda Items 11 and 10 prior to Agenda Item 7.

7. The resulting order of the Agenda Items was 1, 2, 3, 4, 5, 6, 11, 10, 7, 8, 9, 12 and 13.

8. The Delegation of the European Community presented CRD 7 (Annotated Agenda) on 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.

APPOINTMENT OF RAPPORTEUR (Agenda Item 2)

9. The Committee did not appoint a Rapporteur to the Session as nobody volunteered for this task. It agreed that this Agenda Item would be removed from its Agenda in the future.

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1 CX/RVDF 06/16/1; CRD 7 (Division of Competence between the European Community and its Member States).
2 Led by New Zealand.
3 Led by France.

MATTERS REFERRED BY THE CODEX ALIMENTARIUS COMMISSION AND OTHER CODEX COMMITTEES AND TASK FORCES (Agenda Item 3)[4]

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

10. The Secretariat informed the Committee on matters arising from the 28th Session of the Commission and from the 57th Session of the Executive Committee. With regard to the request from the 57th Session of the Executive Committee, it was agreed to discuss the timeframe for the completion of work under each relevant Agenda Item and to communicate the relevant decisions to the Executive Committee.

11. The Committee was informed of the discussion and recommendation made by the 23rd Session of the Codex Committee on General Principles with regard to "Consideration of the Term Interim as Related to the Adoption of Codex Standards and Related Texts".[5]

MATTERS OF INTEREST ARISING FROM FAO AND WHO (Agenda Item 4)[6]

12. The Joint FAO/WHO JECFA Secretariat presented, on behalf of FAO and WHO, working document CX/RVDF 06/16/3. The Committee was informed that output of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) relating to MRL monographs will be published in a new FAO JECFA monographs series.

Expression of the ADI and derivation of the MRL (Practices on rounding of ADI)

13. The Committee was informed that JECFA, at its 66th meeting, had considered the request of the 15th Session of CCRVDF to comment on certain practices on rounding when establishing ADIs and recommending MRLs for veterinary drug residues.

14. JECFA, at its 36th meeting, had considered the expression of the ADI and had decided to express the ADI numerically to only one significant figure. If an ADI is calculated from a NOEL that has more than one significant figure, the ADI would therefore be rounded to one significant figure, consistent with accepted rounding procedures. JECFA has applied its rounding practice to the derivation of ADIs for 25 veterinary drugs; as a result 14 ADIs have been rounded down and 11 ADIs have been rounded up. Most of the veterinary drugs that have been reviewed by JECFA resulted in a calculated ADI of one significant figure without rounding. JECFA concluded that the MRL and the ADI are separate outputs of the risk assessment process and serve different purposes. In addition, the ADI is not directly used in the derivation of the MRL and the rounding practice has no direct consequence on the MRL calculations.

15. JECFA reconfirmed that the rounding practices used in expressing the ADI are scientifically and mathematically sound.

Estimation of chronic dietary intake of residues

16. The Committee was informed about the revised procedure considered and adopted by JECFA at its 66th meeting for the estimation of chronic intake of residues from veterinary drugs in foods. The approach was recommended by the Joint FAO/RIVM/WHO Workshop on the Update of the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs (Bilthoven, the Netherlands, 2005).[7]

17. The new JECFA procedure involves using the median residue concentrations for exposure assessment, it being a more realistic yet conservative estimate instead of using the MRL as a one point estimate. Similar procedures are used by JMPR to estimate intake of pesticide residues from food. The new procedure uses the same formula as used previously for the calculation of the TMDI including factors such as the ratio of marker to total residue concentrations - with the only exception that the median concentration replaces the MRL as point estimate of the residue concentration in the formula. Both figures are obtained from a statistical evaluation of the data.

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4 CX/RVDF 06/16/2.
5 ALINORM 06/29/33, para 148.
6 CX/RVDF 06/16/3.
7 ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf

18. The Committee was informed that for substances on the agenda of the 66th JECFA meeting, both TMDI and the Estimated Daily Intake were calculated. The comparison of the intake with the ADI was in all cases based on the new estimate.

Provision of Scientific Advice

19. The Committee was informed that a new call for experts to serve on JECFA for the period of 2007 - 2011 had been issued and is available at the FAO JECFA website[8]. The call is specifically addressed to experts on assessment of residues of veterinary drugs and derivation of MRLs. In addition, the WHO roster for experts in toxicology for the safety assessment of residues of veterinary drugs in foods is open for applications at any time.

20. The Committee was also informed that a compilation of all procedures followed by FAO and WHO in relation to the provision of scientific advice will be completed and published by the end of 2006. In addition, a report from a recent meeting hosted by FAO and WHO to explore approaches to enhance participation of experts and use of data from developing countries in the provision of international scientific advice had been distributed recently to all Codex contact points.

21. The Committee was informed that FAO/WHO/OIE will conduct an expert consultation on antimicrobial use in aquaculture and antimicrobial resistance in Seoul, Republic of Korea, in June 2006.

Activities of the Food and Environmental Protection Section of the FAO/IAEA Division of Nuclear Techniques in Food and Agriculture[9]

22. The Representative of IAEA informed the Committee of a FAO/IFAH project with inputs from the FAO/IAEA Joint Division to build capacity in sub-Saharan Africa for the quality control of trypanocidal drugs and that, in the future, the scope of the project would be expanded to include the development and transfer of methods for quality control to a range of other veterinary drugs and methods for their residues in foods. The Committee also noted that, in response to a recommendation of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, the FAO/IAEA Joint Programme was planning to hold an inter-regional training course for developing countries on screening and confirmatory methods for veterinary drugs residues. It was further noted the offer to include on the Joint Division's website, Codex analytical methods for veterinary drugs residues in order to enhance the capabilities of developing countries to identify and implement suitable methods in support of residue monitoring plans.

66TH MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (Agenda Item 4a)[10]

23. JECFA evaluated seven veterinary drugs, three antimicrobial agents (Colistin, Erythromycin, Flumequine), two production aids (Melengestrol acetate, Ractopamine hydrochloride), an insecticide (Trichlorfon (metrifonate)) and an anthelmintic (Triclabendazole). For the fourth antimicrobial agent scheduled for evaluation, Tylosin, no data were submitted, and JECFA used this as an example to investigate whether evaluations are possible based on published data in the absence of data submissions from sponsors. The available data were not sufficient for an evaluation of Tylosin. The 66th JECFA also elaborated on a number of general principles.

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8 http://www.fao.org/ag/agn/jecfa/experts_en.stm

9 CRD 5 (Activities of the Food and Environmental Protection Section of the Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture Related to the Work of the Codex Committee on Residues of Veterinary Drugs in Foods).

10 http://www.who.int/ipcs/food/jecfa/summaries/summary66.pdf ; CRD 6 (66th JECFA Assessment of Trichlorfon).

General principles regarding the evaluation of veterinary drugs within the terms of reference of JECFA, including compounds without ADI or MRL

24. The Committee was informed by JECFA of its considerations of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL (Bangkok, 2004), the draft paper prepared by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) Working Group to address recommendations from this workshop in relation to veterinary drugs with no JECFA ADI or MRL, and relevant parts of the Joint FAO/RIVM/WHO Workshop on the Update of the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs. In this context JECFA discussed a number of closely linked issues, including data availability for compounds to be evaluated and the general terms of reference of JECFA.

25. JECFA noted that availability of data is a critical issue, especially for alternative risk assessment approaches, such as benchmark dose or threshold of toxicological concern. JECFA also emphasized the importance of clearly articulated requests by the risk managers, and that based on these requests the nature of the risk assessment determines the data needs. The importance of adherence to the current CCRVDF prioritization criteria was noted. JECFA also emphasized the need for Codex members and commercial entities to fulfil their responsibility in submitting relevant data in a timely manner.

26. JECFA recommended that CCRVDF take an active role in establishing and supporting lists of veterinary drugs in two categories:

i) Veterinary drugs for which significant concerns had been identified, either because of incomplete information or pending resolution of a problem identified in the evaluation;

ii) Veterinary drugs for which these concerns were not addressed, despite requests for data to resolve the outstanding issues. It is recommended that these compounds should not be used in food producing animals until outstanding data are provided and evaluated by JECFA.

27. JECFA noted that because of rapid developments in science, it recognized the continued need for flexibility in its approach, while balancing flexibility with consistency. JECFA recommended convening a working group to develop a general decision tree intended as a tool to assist in assessing different risk assessment options in the evaluation of veterinary drug. The decision tree is envisioned as a flexible document that will be adapted as science advances and considers options such as the use of a threshold of toxicological concern as an alternative to an ADI, and recommendations for analytical methods for the detection of residues of the drug in the absence of a MRL.

Recommendations on principles and methods in derivation of MRLs

28. The Committee was informed that JECFA considered in detail the recommendations of the Joint FAO/RIVM/WHO Workshop on the Update of the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs. Several recommendations resulted in further work, e.g. to elaborate methods to consider setting of acute reference doses for veterinary drugs; for FAO to develop a guidance manual for submission and evaluation of data; and considerations for MRLs in honey.

Use of spreadsheet-based procedure for statistical evaluation of residue depletion data

29. JECFA assessed a workbook that would be of value in helping the experts to statistically evaluate available depletion data during the development of MRL recommendations. This statistical approach will be used in the future whenever it is appropriate and clear reasons should be given when not using it.

Revised approach for the derivation of a microbiological ADI

30. JECFA considered the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) guideline entitled *Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI.* JECFA considered this guideline as a refinement of the current JECFA approach, and in recognition of the importance of international harmonization, agreed to incorporate the VICH guideline in future assessments of antimicrobial compounds to ensure consistency and transparency in the determination of microbiological ADIs.

REPORT OF THE OIE ACTIVITIES, INCLUDING THE HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF VETERINARY MEDICINAL PRODUCTS (VICH) (Agenda Item 5)[11]

31. In order to better protect consumers from potential health hazards associated with animal food, the OIE Members Countries gave the Director-General of that organization the mandate to establish a Working Group to help define a Policy Agenda for the development of standards applicable to the production phase, prior to the slaughtering of animals and the first processing step of animal products. That Working Group includes various WHO, FAO and Codex experts, as well as experts from OIE Member Countries.

32. The main purposes of these standards were to reduce food-born risks for humans associated with hazards during the production phase of foods of animal origin, while strengthening the cooperation between FAO, WHO, the Codex Alimentarius Commission and the OIE, through the development of guidelines for animal production.

33. Having recalled the creation of VICH and named the various Member Countries, the OIE representative noted that the VICH Steering Committee had defined the 2006-2010 VICH strategy, based on the works of a Task Force chaired by OIE. The new topics for future discussion developed by the VICH Steering Committee were presented at the 3rd VICH Conference held in Washington, DC, USA in May 2005.

34. The main technical harmonization progress made since the 15th Session of CCRVDF was introduced. Five guidelines were implemented between December 2004 and March 2006 and two more should be implemented by November 2006.

35. OIE takes great care in ensuring that the VICH process is maintained and even extended in regards to both technical fields covered and geographic impact and will continue to provide its support to the VICH process and will continue to relay the information on VICH to the 167 OIE Members Countries.

36. Having recalled the challenges of antimicrobial resistance for both public health and international trade, the OIE activities implemented in this regard since 1997 were recapped. It was noted that two of the five main guidelines were updated in 2004/2005 to reflect the latest trends and directions and, in particular, to take into account the Codex *Code of Practice to Minimize and Contain Antimicrobial Resistance* (CAC/RCP 61-2005). The revised guidelines were adopted by the May 2005 OIE General Session. All documents are available on the OIE Web site.[12]

37. Given the complexity of the matter, the need to maintain cooperation amongst WHO, FAO, OIE and all the Member States Governments was duly stated.

38. Following the tripartite FAO/WHO/OIE Conferences of December 2003 in Geneva and February 2004 in Oslo, OIE had initiated activities for drafting a list of critically important antimicrobials for veterinary use. The activities undertaken by the *Ad Hoc* Group responsible for work pertaining to the issue of antimicrobial resistance involved OIE Member Countries and various experts. The end results of these activities will be made available to the representatives of OIE Member Countries at the May 2006 General Session. Discussions are also planned for June 2006, in Seoul, Republic of Korea, within the framework of a tripartite FAO/WHO/OIE Expert Consultation on the issue of aquaculture antimicrobial resistance. The purpose of the meeting is to suggest strategies and issue recommendations to help reduce the risks associated with antimicrobial resistance.

39. The Committee noted that OIE deemed still relevant the Oslo Conference recommendation regarding the need for strengthening cooperation between Codex and OIE in order to promote all required synergies and optimize the allocation of resources provided by the various organizations.

40. The Committee expressed its appreciation for the active participation of OIE in the work of Codex and reiterated its support to strengthening this cooperation.

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11 CX/RVDF 06/16/4.

12 www.oie.int

CONSIDERATION OF MAXIMUM RESIDUES LIMITS FOR VETERINARY DRUGS (Agenda Item 6)[13]

Tilmicosin

41. The Committee recalled that the 54th JECFA meeting did not extend the temporary MRL for Tilmicosin in sheep's milk, recommended at its 47th meeting, because the requested information on the results of a study with radiolabelled drug in lactating ewes to determine the relationship between total residues and parent drug in milk had not been submitted.

42. The Committee was informed of the availability of a radiolabelled residue depletion study in dairy cattle and of two residue depletion studies, one in cattle and one in sheep, and that the radio labelled study in cattle could be used to estimate the ratio of marker to total residue for sheep's milk.

43. In view of the strong commitment of the sponsor to make available these studies for further evaluation by JECFA, the Committee agreed to leave in place the temporary MRL for Tilmicosin in sheep's milk until JECFA had evaluated the data and to inform the Commission accordingly. It also agreed to include Tilmicosin for consideration of MRL in sheep's milk in the priority list for JECFA evaluation (see Agenda Item 11).

44. The Committee considered Agenda Items 6a, 6b, 6c and 6d as follows:

Draft MRLs retained at Step 7 by the 15th Session of the Committee[14]

Trichlorfon (metrifonate)

45. The Committee recalled that at its 15th Session it had agreed to hold the MRL for Trichlorfon at Step 7 pending the submission of new data for JECFA re-evaluation. It further noted that the JECFA Secretariat had agreed to reschedule Trichlorfon as a priority substance and to specifically address the toxicological concerns raised by the Delegation of the European Community.[15]

46. The JECFA Secretariat explained that based on the request of the 15th Session a detailed explanation of the scientific concerns raised by the European Community had been received by the JECFA Secretariat and these were considered at the 66th JECFA meeting. The full draft assessment report had been provided to the European Community after the JECFA meeting, and was also distributed as CRD 6 for the 16th CCRVDF. JECFA had responded in detail to all the specific toxicological concerns raised, taking into account all available information, including some new data that had been submitted. In conclusion JECFA confirmed the ADI for Trichlorfon established at the 60th meeting since it did not find any basis for revising it. The previously recommended MRLs were not reconsidered.

47. The Delegation of the European Community acknowledged the submission of the draft JECFA report on the assessment of Trichlorfon and stated that due to the short interval between the 66th JECFA meeting and the 16th Session of CCRVDF, it had not been possible for them to review the JECFA assessment prior to the Session of CCRVDF. The Delegation confirmed the concerns previously expressed regarding the safety of Trichlorfon, in relation to genotoxicity, development toxicity, neurotoxicity and the assessment of pharmacokinetics data, which in their view did not allow the establishment of an ADI and subsequently MRLs for Trichlorfon. In addition, the Delegation had expressed concern that for the main metabolite, dichlorvos, no reliable ADI had been established.

48. Therefore the Delegation of the European Community proposed to defer the discussion on the MRLs until the next Session of the Committee in order to better examine the JECFA report. The position of the European Community was supported by two other delegations.

49. Other delegations were in favour of advancing the MRL because: all concerns as to the safety of Trichlorfon had been adequately addressed by JECFA; the conclusions of JECFA were clear and no new data are available to consider a further evaluation; the product was in use in many countries; and further delay in recommending a MRL in milk for this substance could have serious implication on trade.

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13 CX/RVDF 06/15/5.

14 ALINORM 05/28/31, Appendix IV; CRD 6 (66th JECFA Draft Safety Assessment of Trichlorfon).

15 ALINORM 05/28/31, para. 74.

50. The Committee agreed to advance the MRL for Trichlorfon to Step 8 and noted the reservation of the European Community and its Member States to this decision for the reasons mentioned above.

Draft MRLs advanced to Step 6 by the 28th Session of the Commission[16]

51. The Committee noted that the 28th Session of the Codex Alimentarius Commission had adopted the proposed draft MRLs for Flumequine in Black tiger shrimp muscle, for Pirlimycin in cattle tissues and cattle milk, for Cypermethrin and alpha-Cypermethrin in cattle and sheep tissues and for Doramectin in cow's milk at Step 5 and had advanced them to Step 6.[17]

Flumequine

52. The JECFA Secretariat informed the Committee that the 66th JECFA meeting had evaluated the analytical method submitted as being adequate, but that no information was made available on the registered use of Flumequine in shrimps. JECFA confirmed the temporary MRL for Flumequine in Black tiger shrimp and, in response to the request from the 15th CCRVDF, extended it to all freshwater and marine shrimps.

53. The Committee noted that there was no food safety concern for the temporary MRL and that information on registered use of Flumequine in Black tiger shrimp and/or shrimps was essential to decide on its further progress.

54. The Committee also noted the inability to ascertain at the present Session whether the use of Flumequine in Black tiger shrimp and/or in shrimps was registered in any country and the consequences of recommending MRLs for non-registered substances. Therefore, it agreed to retain the MRLs for Flumequine in muscle of Black tiger shrimp and shrimps at Steps 7 and 4, respectively. The Committee agreed to ask the Codex Secretariat to issue a Circular Letter requesting information on registered use of Flumequine with the understanding that, if this information is not provided, it will discontinue work on these MRLs at its next Session.

Pirlimycin

55. The Committee supported the MRLs for Pirlimycin in cattle tissues, i.e. muscle, liver, kidney and fat, as proposed by the 62nd JECFA meeting, and agreed to advance them to Step 8.

56. With regard to the MRL for cow's milk, many delegations expressed their concern that the MRL was based on food processing and/or manufacturing consideration, i.e. the potential inhibition of dairy starter cultures, and not on food safety considerations. They noted that the recommended MRL would result in longer discard time, leading to unnecessary discard of milk. They were of the opinion that Codex MRLs should be established as international standards that are protective of human health and should not be based on the facilitation of certain food production or processing techniques that are not associated with food safety. These delegations proposed a MRL of 200 µg/kg based on food safety, which along with the tissue MRLs resulted in a TMDI compatible with the ADI.

57. Other delegations were in support of the MRL of 100 µg/kg, based on technological considerations as proposed by the 62nd JECFA. They noted that, accordingly to the Codex definition, a MRL also takes into account food technological aspects.

58. The JECFA Secretariat clarified that JECFA considers effects on starter cultures as the basis of an MRL based on the request of CCRVDF and urged the Committee to give clear directions on whether such food technological effects should continue to be considered or not.

59. The Committee noted that the decision to calculate MRLs on the basis of food safety or food processing technological consideration was a risk management policy decision to be considered by the Committee in the future.

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16 ALINORM 05/28/31, Appendix V; CL 2005/35-RVDF (Request for Comments at Step 6 of draft MRLs for Veterinary Drugs); CX/RVDF 06/16/6 (Comments of Argentina, Australia, Brazil, Canada, European Community, Japan, United States of America, Venezuela and IFAH); CX/RVDF 06/16/6, Add.1 (Comments of United States of America).

17 ALINORM 05/28/41, para. 76 and Appendix VI.

60. The Committee agreed to advance to Step 8 an MRL based on food safety consideration of 200 µg/kg with the following footnote "JECFA evaluated the effect of pirlimycin residues on starter cultures and for this reason recommended an MRL of 100 µg/kg of milk. Codex Members may therefore adapt national/regional MRLs in order to address this technological aspect for trade of fresh liquid milk intended for processing using starter culture".

Cypermethrin and alpha cypermethrin

61. The Committee agreed to advance the MRLs proposed by the 62nd JECFA for Cypermethrin and alpha Cypermethrin to Step 8.

Doramectin

62. The Committee was in support of advancing the MRL for Doramectin in cattle's milk. However, some Delegations expressed concern that the footnote in the report of the 62nd JECFA meeting about the long milk discard time and the assumption that this would not be consistent with good veterinary practice, could raise unnecessary concerns for food safety in international trade. Other delegations supported the retention of the footnote as it provided good guidance to those countries where the drug was not authorised for use in lactating cows or it was recently introduced. As a way to further progress, the Committee agreed to simplify the footnote to read "Depending on the route and/or time of administration, the use of Doramectin in dairy cows may result in extended withdrawal periods in milk. This may be addressed in national/regional regulatory programmes".

63. The Committee agreed to advance the MRLs for Doramectin in cattle's milk to Step 8 with the revised footnote.

Proposed Draft MRLs retained at Step 4 by the 15th Session of the Committee[18]

Ractopamine

64. The Committee agreed to advance the MRLs proposed by the 62nd JECFA meeting for Ractopamine in cattle and pig's tissues to Step 5, as there was no consensus to advance them to Step 5/8.

Draft and Proposed Draft MRLs recommended by the 66th JECFA meeting[19]

65. The Committee recalled that at its 15th Session it had agreed to include in the list of priorities for evaluation or re-evaluation by JECFA: Colistin, Triclabendazole, Melengestrol acetate, Tylosin, Erythromycin, Enrofloxacin, Trichlorfon and Ractopamine.[20] It noted that all these substances, with the exception of Enrofloxacin and Tylosin (see para. 23), had been considered by the 66th JECFA meeting and that the JECFA recommendations had been circulated for comments in document CX/RVDF 06/16/7.

Colistin

66. The Committee agreed to advance the MRLs proposed by the 66th JECFA meeting for Colistin in cattle, sheep, goat, pig, chicken, turkey and rabbit's tissues, cattle and sheep's milk and in chicken's eggs to Step 5.

Erythromycin

67. In view of the need by some delegations to consider in detail the full JECFA evaluation, the Committee agreed to circulate the MRLs for Erythromycin in chicken and turkey's tissues and chicken's eggs for comments at Step 3 and further consideration at its next Session.

Melengestrol acetate

68. The Committee recalled that at its previous Session, due to an inaccuracy in the calculation of the TMDI of Melengestrol acetate (MGA), it had been decided to request JECFA to reassess the recommended MRLs from the 62nd JECFA meeting and to circulate for comments at Step 6 the MRLs from the 66th JECFA meeting for consideration at the present Session.[21]

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18 ALINORM 05/28/31, Appendix VI; CRD 8 (Comments of Vietnam).
19 CX/RVDF 06/16/7; CX/RVDF 06/16/7, Add.1 (Comments of Canada and European Community).
20 ALINORM 05/28/31, para. 171 and Appendix IX.
21 ALINORM 05/28/31, paras 61-62.

69. The Delegation of the European Community referring to its written comments contained in CX/RVDF 06/16/7, Add.1, stated that the MGA was evaluated by JECFA as growth promoters and that such use of hormones with estrogenic, androgenic or gestagenic action was prohibited in the European Union. The provision was permanent for Oestradiol 17beta and provisional for the other hormonal substances. The 2002 review of the Scientific Committee on Veterinary Measures relating to Public Health considered the report on MGA prepared by the 54th meeting of JECFA and observed that it provides a comprehensive review of the pharmacokinetic/toxicokinetic parameters and toxicological properties of MGA in various species. The Delegation argued, however, that no original data were presented in the review and the majority of references were reports that had not been published in the peer-reviewed scientific literature. Therefore, for MGA, concerns remained that excess intake of hormone residues and their metabolites, endocrine, developmental, immunological, neurobiological, immunotoxic, genotoxic and carcinogenic effects could be envisaged, in particular for susceptible risk groups. For these reasons, the European Community could not support the adoption of the MRLs proposed by the 66th JECFA. This position was supported by two other delegations.

70. The JECFA Secretariat pointed out that the 66th JECFA meeting had only evaluated the residue part, according to the request of CCRVDF and had recalculated the MRLs accordingly.

71. The Delegation of the United States of America explained the scientific review conducted by JECFA regarding MGA. It was noted that the review considered all the relevant toxicology issues that have been raised regarding MGA. JECFA concluded that the most relevant and sensitive end point for an ADI was its hormonal activity. Detailed studies were described on identifying the metabolites where sufficient amounts of residues were available to permit identification and measurements of hormonal activity. The Delegation noted that the recommended MRLs considered all the relevant metabolites with hormonal activity. JECFA therefore concluded that the recommended MRLs were consistent with the upper bound of the ADI and would protect public health and facilitate fair trade. On this basis, the Delegation of the United States of America supported the advancement of the recommended MRLs to Step 8.

72. Other delegations supported the advancement of the MRLs for MGA in cattle tissues as recommended by the 66th JECFA meeting. They noted that: the drug had been in use since many years and was registered in many countries; the low level of residue of MGA in muscle; the safety profile of MGA had been thoroughly examined by JECFA, which concluded that there was no food safety concern; no new data were available to justify a further JECFA examination; the compound had been considered by the Committee for a long time and all food safety concerns expressed had been addressed by JECFA; and the opposition to the advancement of the MRLs was not based on valid scientific concerns.

73. As consensus could not be reached on the advancement of the MRLs for MGA at the present Session, the Committee agreed to retain the MRLs at Step 7 for further consideration at its next Session and to inform the Executive Committee accordingly.

Triclabendazole

74. The Committee recognised the need to study the differences between the old (40th JECFA) and the recent (66th JECFA) evaluation of Triclabendazole.

75. In response to comments made by the Observer from IFAH regarding communication between the sponsor and JECFA experts, the JECFA Secretariat explained that interaction between JECFA experts and sponsors are encouraged during the assessment process, as necessary. The sponsors are provided with the final draft monograph prepared by the experts for factual comments. This procedure was followed also in the assessment process for Triclabendazole.

76. In view of the need to consider in detail the full JECFA evaluation, the Committee agreed to circulate the MRLs for Triclabendazole in cattle, sheep and goat's tissues for comments at Step 3 and further consideration at its next Session.

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

77. Draft and proposed draft MRLs forwarded to the 29th Session of the Commission for adoption at Step 8 and at Step 5 are attached as Appendices II and IV, respectively. Draft and proposed draft MRLs retained at Step 7 and at Step 4 are attached as Appendices III and V, respectively. Proposed draft MRLs to be circulated for comments at Step 3 are attached as Appendix VI.

PROPOSED DRAFT REVISED GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAMME FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN FOODS (Agenda Item 7)[22]

78. The Committee recalled that at its 15th Session, it had agreed to return the proposed draft revision of the Guidelines to Step 2 for redrafting by a Working Group led by New Zealand.[23]

79. The Delegation of New Zealand, leader of the *ad hoc* Working Group on Agenda Item 7 (see para. 5), introduced CRD 15. The *ad hoc* Working Group had reviewed the Guidelines to take into account all comments submitted and made changes to further simplify, clarify and improve the text. In particular the *ad hoc* Working Group had:

- Revised the title and subsequent references to reflect that the Guidelines were intended for use by national regulatory bodies for the purpose of being able to provide food safety assurances;
- Deleted the definitions of veterinary drug, residue and food producing animal as they were effectively covered in the Codex Procedural Manual;
- Made more explicit reference to: compliance with MRLs of veterinary drugs reflecting the legal status of these standards in the national/regional legislation; relative accountabilities of exporting countries and the rights of importing countries; and the necessity of controls and assurances associated with substances which may be prohibited by national regulatory bodies;
- Removed any remaining references to pesticides, contaminants or feed;
- Put in brackets several sections for further discussion by the Committee.

80. The Committee endorsed all changes made by the *ad hoc* Working Group. It focused its discussion on sections that were put in square brackets and agreed to the following:

Paragraph 1

81. The paragraph was deleted as unnecessary.

Paragraph 70 (renumbered paragraph 66)

82. The Committee revised the paragraph to improve its clarity.

Paragraph 89

83. The Committee noted that the first sentence of the paragraph contained a useful reference for risk managers on measurement uncertainty, while the second sentence was dealing with the specific actions, which was relevant to the technical annexes of the Guidelines. It agreed to delete the paragraph and to include a reference to measurement uncertainty of analytical results in the preceding paragraph (renumbered paragraph 84).

Paragraph 112 (renumbered paragraph 106)

84. The Committee noted that the text in square brackets included two issues: the need to use fully validated analytical methods and provisions for substances which pose a risk to human health. The Committee retained the first part of the sentence "It is important that any analytical methods used are fully validated for the specific matrix analyzed" and deleted the remaining part of the sentence as it felt that it was premature to include in the Guidelines provision for "regulatory action levels" of substances which are of health concern. It agreed that this issue needed further discussion outside the current revision of the Guidelines and that the inclusion of language in this regard could be considered in the future. It further agreed that this issue be considered by the Working Group on Residues of Veterinary Drugs without ADI/MRL (see para. 134).

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22 CX/RVDF 06/16/8; CX/RVDF 06/16/8, Add. 1(Comments at Step 3 of Australia, Brazil, Canada, European Community; United States of America and IDF); CRD 9 (Comments of IFAH); CRD 10 (Comments of Thailand); CRD 11 (Comments of Philippines); CRD 12 (Comments of South Africa); CRD 13 (Comments of Indonesia); CRD 15 (Report of the *ad hoc* Working Group on Agenda Item 7).

23 ALINORM 05/28/31, para. 123.

85. The Committee agreed with the revised text, although it recognised that additional work was still needed to improve paragraph ordering and readability of the text.

Status of the proposed draft Revised Guidelines for the Establishment of a Regulatory Program for the Control of Veterinary Drug Residues in Foods

86. The Committee agreed with the recommendation of the *ad hoc* Working Group to merge the revised Guidelines and the technical annexes (see Agenda Item 8) with the associated deletion of the redundant text and to forward the entire renamed "Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programme Associated with the Use of Veterinary Drugs in Food Producing Animals" to the 29th Session of the Codex Alimentarius Commission for adoption at Step 5 (see Appendix VII).

87. It further agreed to inform the 58th Session of the Executive Committee that this work would be completed by its next Session.

PROPOSED DRAFT REVISED PART I, II, III OF THE CODEX GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAMME FOR THE CONTROL OF VETERINARY DRUGS RESIDUES IN FOODS (Agenda Item 8) [24]

88. The Committee recalled that at its 15th Session it had agreed to return the proposed draft Revised Part II of the Guidelines to Step 2, and had agreed that a Working Group, led by Canada, would redraft all sections on methods of analysis and sampling in the Guidelines (Part I, II and III), for comments and consideration at the present Session[25].

89. The Chair of the *ad hoc* Working Group on Methods of Analysis and Sampling introduced the discussion and the relevant recommendation of the Working Group on this item. The Working Group had reviewed all comments submitted and amended the text accordingly and put in square brackets the definition of "lot" for further consideration.

90. The Committee noted that the *ad hoc* Working Group had discussed proposals related to the development of methods outside the scope of supporting an ADI/MRL and the use of the term "Recommended Performance Limits (RPL)" applicable to such methods. The Working Group did not formulate any recommendation because it felt that it was not within the assignment received. In order to address these proposals, the Committee agreed to request the Working Group on Residues of Veterinary Drugs without ADI/MRL to recommend the technical inputs required by the Working Group on Methods of Analysis and Sampling in support of the future work of the Committee on residues of veterinary drugs without an ADI/MRL (see para. 134).

91. The Committee endorsed the revised text as proposed by the *ad hoc* Working Group and agreed to the following changes:

Part I - Sampling for the Control of Residues of Veterinary Drugs in Foods

92. The Committee deleted the entire section in accordance with the previous decision regarding the merging of the Guidelines and the technical annexes (see para. 86).

Appendix I

93. The Committee agreed to put the definitions of "lot" and "consignment" in square brackets and to revisit them at its next Session in light of the definitions and work developed by the Codex Committees on Food Labelling and Food Import and Export Inspection and Certification Systems and of the OIE work on animal identification. It noted that this decision would also apply to the definitions of "lot" and "consignment" in Appendix B.

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24 CX/RVDF 06/16/9, CX/RVDF 06/16/9, Add.1 (Comments at Step 3 of Argentina, Australia, Brazil, Canada, European Community and United States of America); CRD 1 (Report of the *ad hoc* Working Group on Methods of Analysis and Sampling); CRD 9 (Comments of IFAH). CRD 13 (Comments of Indonesia); CRD 16 (Comments of United States of America).

25 ALINORM 05/28/31, para. 132.

Part III – Method Development and Validation Considerations for Residue Control Methods

94. The Committee agreed to the proposal of the Delegation of the United States of America to introduce a new paragraph that defines an equivalent material, after paragraph 132 in Section III.4.1 "Selection of Appropriate Test Material for Validation", as contained in CRD 16. The term "type II or III methods" was changed to "level II or III methods" as more appropriate.

Status of the proposed draft revised Parts I, II and III of the Codex Guidelines for the Establishment of a Regulatory Programme for the Control of Residue of Veterinary Drugs in Foods

95. The Committee reaffirmed its previous decision concerning the merging of the revised Guidelines (see Agenda Item 7) and this document (see para. 86).

RISK MANAGEMENT METHODOLOGIES, INCLUDING RISK ASSESSMENT POLICIES, IN THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (Agenda Item 9) [26]

96. The Committee recalled that at its 15th Session it had agreed that the discussion paper on risk management policies should be redrafted as a working document for inclusion in the Procedural Manual and that a Working Group, led by France, would redraft the document taking into account the written comments, its discussion and the recommendations of the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, where applicable.[27]

97. The Delegation of France, leader of the *ad hoc* Working Group on Agenda Item 9 (see para. 5), introduced CRD 14. The Working Group reviewed the proposed draft Risk Analysis Methodologies in the Codex Committee on Residues of Veterinary Drugs in Foods (including its Annex) and the proposed draft Risk Assessment Policy for the Setting of MRLs in Food, taking into consideration the comments submitted and made necessary amendments accordingly.

98. The Committee considered the two texts paragraph by paragraph and agreed to the following changes.

Proposed draft Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods (including its Annex)

Section 1 - Purpose- Scope

99. The Committee deleted "with particular emphasis on Risk Assessment Policies" to emphasise that the scope of the document was to specify Risk Analysis Principles applied by the Committee and for consistency with the scope of Risk Analysis Principles developed by other Codex Committees.

Section 2 - Parties Involved

100. The Committee acknowledged that its risk management recommendations should be based on JECFA risk assessment. In paragraph 3, it deleted the last part of point (d), for consistency with its terms of reference. Regarding the proposal to use national/regional assessment for JECFA evaluation, the Committee noted that national/regional assessment contain proprietary information and could only be submitted to JECFA with the agreement of the sponsor. Therefore, it agreed to delete paragraph 2c.

101. The Committee deleted the second sentence of paragraph 2f (renumbered paragraph 7) because it was a direct quotation of the Codex *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius*.

Section 3.1 - Preliminary risk management activities

102. The Committee qualified the term "Risk profile" by inserting "preliminary" in the interest of clarity. It agreed to apply this change throughout the text.

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[26] CX/RVDF 06/16/10, CX/RVDF 06/16/10, Add.1 (Comments of Argentina, Australia, Brazil, Canada, Japan and United States of America); CX/RVDF 06/16/10, Add.2 (Comments of JECFA Secretariat); CRD 14 (Report of the Working Group on Risk Management Methodologies, Including Risk Assessment Policies).

[27] ALINORM 05/28/31, paras 152-153.

Section 3.1.2 - Identification of a Food Safety Problem (establishment of the priority list)

103. The Committee agreed to add "a Member has proposed the compound for evaluation" and "a Member has established good veterinary practice with regard to the compound" to the criteria to be met for inclusion on the priority list.

Section 3.1.6 – Consideration of the Result of the Risk Assessment

104. Paragraph 16 was amended to better reflect the current practice used when insufficient data are submitted to JECFA. Paragraph 18 was amended to better clarify the role of JECFA in providing risk management options to CCRVDF for its consideration.

Section 3.2 – Evaluation of Risk Management Option

105. The Committee aligned the language of paragraph 23 with the Guidelines for the Establishment of a Regulatory Programme for the Control of Residue of Veterinary Drugs in Foods (see Agenda Items 7 and 8) and simplified the text to refer only to the availability of analytical methods.

Section 3.3 – Monitoring and Review of Decision Taken

106. Paragraph 25 was deleted because it was inconsistent with the recommendation of the 23rd Session of the Codex Committee on General Principles regarding principles for the adoption of "temporary or interim" food safety standards. [28]

107. In paragraph 26, the term "risk analysis" was changed to "risk assessment" for clarity.

Annex – Template for Information Necessary for Prioritization by CCRVDF

108. The Committee agreed to change the title of the Annex to "Template for Information Necessary for Prioritization by CCRVDF. In point 14, the Committee added reference to Regional MRLs to take into account that Codex membership also includes a regional economic integration organization. The examples of data available were broadened to include pharmacology and analytical methods.

109. The Committee agreed to use this template in the Circular Letter requesting "Comments/Information for the Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation by JECFA".

Proposed Draft Risk Assessment Policy for the Setting of MRLs in Food

110. In paragraph 12 (renumbered paragraph 3), the term "information" was changed to "data" for consistency. The title of the last section was changed to "Expression of risk assessment results in terms of MRLs" to better reflect its content. Paragraph 15 (renumbered paragraph 6) was amended to clarify that JECFA should clearly describe in its report situations where the calculation of MRLs to be compatible with the ADI might be associated with a lengthy withdrawal period.

Status of the proposed draft Risk Management Methodologies, including Risk Assessment Policies in the Codex Committee on Residues of Veterinary Drugs in Foods

111. The Committee agreed to forward the renamed Risk Analysis Principles applied by the Codex Committee on Residues of Veterinary Drugs in Foods and the Risk Assessment Policy for the Setting of MRLs in Food to the Codex Alimentarius Commission, through the Codex Committee on General Principles, for adoption and inclusion in the Codex Procedural Manual (see Appendices VIII and IX).

Future Work on Risk Management Option

112. The Committee acknowledged that there was a need for further discussion related to risk management options including risk assessment policy and that a possible mechanism to facilitate discussion on this issue might be a physical Working Group meeting before the Session to consider specific issues related to risk management.

113. The Committee agreed to establish an electronic Working Group, led by France[29], to prepare a Discussion Paper to identify risk management topics and options to be considered at the next Session of the Committee. The electronic Working Group would work in English only.

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28 ALINORM 06/29/33, para. 148.

114. The Committee noted that active participation of the members of the electronic Working Group was required, especially in identifying the risk management issues and their rationale, in order to produce a useful document for consideration of the Committee.

METHODS OF ANALYSIS FOR RESIDUES OF VETERINARY DRUGS IN FOODS (Agenda Item 10) [30]

115. The Committee recalled that at its 15th Session, it had not been possible to finalise the list of methods of analysis for veterinary drugs to be submitted at the Commission and it had agreed that the list prepared for and recognized at the Session would be circulated for comments and the inclusion of additional methods and considered further at the present session, with a view to its finalization.[31]

116. The Chair of the *ad hoc* Working Group on Methods of Analysis and Sampling, Dr James MacNeil (Canada), presented the report of the Working Group held prior to the Session, that had addressed the proposed draft revised Part I, II, III of the Codex *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* (see Agenda Item 8) and the list of methods of analysis identified as suitable to support the MRLs for Veterinary Drugs.

117. The Committee noted that the *ad hoc* Working Group had amended the list to correct several minor errors or omissions and had considered new methods submitted in response to CL 2005/10-RVDF, which included: new methods to support existing MRLs for veterinary drugs, and methods for compounds for which MRLs do not exist or for matrices for which there are no current MRLs for the substances.

118. The *ad hoc* Working Group reorganised the list to include two separate Annexes with information on methods for: i) those substances and matrices for which validated methods were still required; and ii) those substances or matrices without MRLs.

119. The Committee endorsed the recommendation of the *ad hoc* Working Group to ask the Codex Secretariat to issue a Circular Letter requesting that members and observers review the list of methods; review and update any addresses of contact points for information; advise of any methods for which they are no longer able to provide information; and provide information on substances and matrices for which validated methods are still required.

120. The Committee agreed to forward to the 29th Session of the Codex Alimentarius Commission the Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs (see Appendix X).

121. The Committee agreed to reconvene the *ad hoc* Working Group on Methods of Analysis and Sampling, under the co-Chairmanship of Canada and United Kingdom, prior to its next Session to continue work on the identification of suitable methods of analysis for residues of veterinary drugs in foods on the basis of information received in response to the Circular Letter. It was noted that the *ad hoc* Working Group would work in English, French and Spanish.

122. The Committee acknowledged Dr Rainer Stephany´s (the Netherlands) significant contribution and dedicated services to CCRVDF and to the *ad hoc* Working Group on Methods of Analysis and Sampling over the past two decades.

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29 With the assistance of Australia, Austria, Brazil, Canada, Ireland, Japan, Malaysia, Netherlands, New Zealand, Republic of Korea, Sweden, Thailand, United Kingdom, United States of America, IAEA, CI, IDF and IFAH.

30 CL 2005/10-RVDF (Methods of Analysis for Veterinary Drugs – Request for Information/Comments); CX/RVDF 06/16/11 (Comments/Information of Argentina, Canada, European Community, Pakistan, Thailand and Venezuela); CRD 1 (Report of the *ad hoc* Working Group on Methods of Analysis and Sampling); CRD 3 (Canada - Additional information).

31 ALINORM 05/28/31, paras 158-159.

CONSIDERATION OF THE PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION (Agenda Item 11) [32]

123. The Chair of the *ad hoc* Working Group on Priorities, Dr Peter Dagg (Australia) presented CRD 2. The Working Group had considered responses to CL 2005/43–RVDF and the Report of the Working Group on Residues of Veterinary Drugs without ADI/MRL.

Response to CL 2005/43 – RVDF

124. It was noted that no comments/information had been submitted for compounds to be evaluated/re-evaluated by JECFA.

Report of the Working Group on Residues of Veterinary Drugs without ADI/MRL

125. The Committee noted that the *ad hoc* Working Group had significant discussion on the report of the Working Group on Residues of Veterinary Drugs without ADI/MRL and how further progress might be made. The Working Group on Priorities identified the following major issues: the problem of data availability when compounds are proposed and potential sponsors are unwilling to submit data packages; the possibility of using new ways of risk assessment for veterinary drugs and the setting of MRLs; the need for JECFA to receive appropriate data for its assessments; whether any "negative list" of veterinary drugs of human health concern should be developed; and whether any compounds not assessed by JECFA should be included in such a list.

126. The Working Group could not reach any agreement on the development of a "negative list" and, as a compromise position, it proposed to develop criteria for risk management options for those compounds for which an ADI and/or MRL cannot be set and to continue to work only on Annex III of the Report of the Working Group on Residues of Veterinary Drugs without ADI/MRL.

127. To further prioritize compounds in Annex III, the Working Group also proposed to consider three categories of compounds: i) compounds which JECFA has assessed and identified human health concerns; ii) compounds which require only a small amount of data to complete the JECFA assessment, and iii) compounds which are of major significance to certain countries because of human health or trade concerns.

128. With regard to the possibility to develop "interim" MRLs based on national assessment, the Working Group acknowledged the need for a transparent and independent assessment to produce international MRLs. The Committee was also informed of the decisions of the 38th Session of the Codex Committee on Pesticide Residues to discontinue the "Pilot Project for the Estimation of National MRLs as Interim Codex MRLs for Safer Replacement Pesticides".[33] The recommendations of the 23rd Session of the Codex Committee on General Principles regarding the adoption of "temporary or interim" food safety standards were also noted. [34]

129. The Committee considered the preliminary priority list of veterinary drugs requiring evaluation or re-evaluation prepared by the *ad hoc* Working Group on Priorities. It agreed to the recommendation of the JECFA Secretariat to revise the list to include more details regarding the issues to be addressed, the identification of target species/tissues and data availability.

130. The Committee agreed to add to the list of veterinary drugs proposed by the *ad hoc* Working Group the following proposals: Tilmicosin in sheep's milk (United States of America); Tylosin in cattle tissues (Germany); Nitrofurans in honey (France); and Xylazine in deer tissues (New Zealand).

131. The Observer from IFAH confirmed its commitment to consult with sponsors, who are IFAH members, regarding the availability of data for the substances and to work with sponsors to ensure the submission of data, but cautioned that there was likely to have some difficulties for the submission of data of older antimicrobials.

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[32] CL 2005/43-RVDF (Request for Comments/Information on Priority List of Veterinary Drugs Requiring Evaluation or Reevaluation), CX/RVDF 06/16/12 (not issued); CX/RVDF 06/16/13 Part I and Part II (Report of the Working Group on Residues of Veterinary Drugs without ADI/MRL); CRD 2 (Report of the *ad hoc* Working Group on Priorities); CRD 4 (Comments of the United States of America); and Addendum 2 to CRD 2 (Revised Annex I to CRD 2: Veterinary Drugs Identified as Priority for Evaluation by JECFA).

[33] ALINORM 06/29/24, para. 201.

[34] ALINORM 06/29/33, para. 148.

132. The Committee noted the difficulties of some developing countries to meet all the requirements for nomination and inclusion of compounds in the priority list. In this regard, the JECFA Secretariat stated that confirmation of data availability was a prerequisite for inclusion of substances in the priority list and highlighted the need for countries to consult with industry prior to nomination of substances.

133. The Committee agreed to forward the priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA, as attached in Appendix XI. It was agreed that the availability of data and types of data for Dexamethasone, Kanamycin, Bacitracin, Flavophospholipol, Nitrofurans and Malachite Green should be confirmed to the JECFA Secretariat by July 2006. Substances for which data availability cannot be confirmed will not be scheduled for evaluation by JECFA.

134. The Committee agreed to re-establish the physical Working Group on Residues of Veterinary Drugs without ADI/MRL led by the European Community[35] to consider Annex III (Starting Point for a Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation by JECFA) of CX/RVDF 06/16/13. In particular, the Working Group will: i) give further consideration to the prioritization of compounds on the list and update the list; ii) consider management option for compounds to be evaluated by JECFA where a management decision is pending; and iii) provide guidance on practical analytical methods suitable for use by national regulatory authority for these compounds (see para. 90). It was agreed that the physical Working Group would meet in the first months of 2007 and work in English, French and Spanish.

135. The Committee also agreed to reconvene the *ad hoc* Working Group on Priorities prior to its next Session, under the chairmanship of Australia, to consider proposals for compounds to be evaluated or re-evaluated by JECFA and the report of the physical Working Group on Compounds with no ADI/MRL (see para. 134). It was noted that the *ad hoc* Working Group would work in English, French and Spanish.

OTHER BUSINESS AND FUTURE WORK (Agenda Item 12)

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

DATE AND PLACE OF NEXT SESSION (Agenda Item 13)

137. The Committee was informed that its 17th Session was tentatively scheduled to be held in September 2007, subject to further discussion between the Codex and United States of America Secretariats.

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35 With the assistance of Australia, Brazil, Canada, Costa Rica, Denmark, France, Germany, Japan, Republic of Korea, Mexico, Malaysia, New Zealand, Thailand, Sweden, United Kingdom, United States of America, FAO, WHO, CI and IFAH.

SUMMARY STATUS OF WORK

SUBJECT MATTER	STEP	ACTION BY:	DOCUMENT REFERENCE (ALINORM 06/29/31)
Draft Maximum Residue Limits for: - Trichlorfon - Pirlimycin - Cypermetrhrin and alpha-cypermethrin - Doramectinl	8	29th CAC	Para. 77 and Appendix II
Draft Maximum Residue Limits for: - Flumequine (Black tiger shrimp) - Melengestrol acetate	7	17th CCRVDF	Para. 77 and Appendix III
Proposed Draft Maximum Residue Limits for: - Colistin - Ractopamine	5	29th CAC	Para. 77 and Appendix IV
Proposed 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	5	29th CAC	Para. 86 and Appendix VII
Proposed Draft Maximum Residue Limits for: - Flumequine (shrimps) - Ractopamine	4	17th CCRVDF	Para. 77 and Appendix V
Proposed Draft Maximum Residue Limits for: - Erythromycinne - Triclabendazole	3	Members/ Observers	Para. 77 and Appendix VI
Priority List of Veterinary Drugs Requiring Evaluation of Re-evaluation	1	29th CAC	Para. 133 and Appendix XI
Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Foods	-	30th CAC	Para. 111 and Appendix VIII
Risk Assessment Policy for the Setting of MRLs in Food	-	30th CAC	Para. 111 and Appendix IX
Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs	-	29th CAC	Para. 120 and Appendix X
Discussion Paper to on Risk Managements Topics and Options for the CCRVDF	-	Working Group	Para. 113
Report of the Working Group on Residues of Veterinary Drugs without AD/MRL	-	Working Group	Para. 134

Appendix I

LIST OF PARTICIPANTS - LISTE DE PARTICIPANTS - LISTA DE PARTECIPANTES

Chairperson
President
Presidente

Stephen Sundlof
Director, Center for Veterinary Medicine
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
7519 Standish Place, MPN4
Rockville, MD 20855
United States
Tel: 240-276-9000
Fax: 240-276-9001
Stephen.Sundlof@fda.hhs.gov

Co-Chairperson
Co-President
Co-Presidente

Octavio Carranza de Mendoza
Director of Import, Export Services and Animal Certification
Department of Agriculture
SAGARPA – SENASICA
Municipio Libre # 377, Piso 7 ala "A"
Col. Santa Cruz Atoyac, Del. Benito Juárez,
C.P. 03310
México, D.F.
Mexico
Tel: (52) 55 91 83 1000 Ext. 33946
Fax: (52) 55 91 83 1000 Ext. 33945
carranza@senasica.sagarpa.gob.mx

Assistant to the Chairperson
Assistant Au President
Asistente al Presidente

Merton Smith
Assistant to the Chairperson
Special Assistant for International Activities
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
7519 Standish Place, MPN4
Rockville, MD 20855
United States
Tel: 240-276-9025
Fax: 240-276-9001
Merton.Smith@fda.hhs.gov

AUSTRALIA - AUSTRALIE

Bob Biddle
Deputy Chief Veterinary Officer
Product Integrity Animal and Plant Health
Australian Government Department of Agriculture Fisheries and Forestry
GPO Box 858
Canberra ACT
Australia
Tel: +61 2 6272 5364
Fax: +61 2 6272 3150
bob.biddle@daff.gov.au

Jim Derrick
Manager
Meat Programs
National Residue Survey
Australian Government
Department of Agriculture Fisheries & Forestry
GPO Box 858
Canberra ACT 2601
Australia
Phone: +61 2 6272 4019
Fax: +61 2 6272 4023
jim.derrick@daff.gov.au

Peter Dagg
Veterinary Officer
Australian Government Department of Agriculture, Fisheries & Forestry
GPO Box 858 Canberra ACT 2601
Australia
Phone: +61 2 6272 5975
Fax: +61 2 6272 3372
peter.dagg@daff.gov.au

E. John Murby
Principal Chemist
Chemical Reference Methods
National Measurement Institute
PO Box 385
Pymble NSW 2073
Australia
Phone: +61 2 94490193
Fax: +61 2 94491653
john.murby@measurement.gov.au

Lee Cook
Veterinary Officer
Biological and Chemical Risk Management
New South Wales Department of Primary Industries
Locked Bag 21 Orange NSW 2800
Australia
Phone: +61 2 6391 3722
Fax: +61 2 6391 3740
lee.cook@dpi.nsw.gov.au

Peter Holdsworth
Chief Executive Officer
Animal Health Alliance (Australia) Ltd
Locked Bag 916
Canberra ACT 2601
Australia
Phone: +61 2 62579022
Fax: +61 2 6257 9055
peter.holdsworth@animalhealthalliance.org.au

AUSTRIA - AUTRICHE

Thomas W. Kuhn
Head of the Delegation
Austrian Agency for Health and Food Safety
Competence Centre Veterinary Drugs and Hormones
Spargelfeldstrasse 191, A-1226 Vienna
Austria
Tel: 43 0 505 55-32600
Fax: 43 0 505 55-32630
thomas.kuhn@ages.at

Eugen Obermayr
Austrian Agency for Health and Food Safety
Pharm Mes
Shnirchgasse 9
1030 WIEN
Austria
Tel: 43 50555 36670
eugen.obermayr@ages.at

Philip Landon
Administrator
The General Secretariat of the Council of the European Union
Rue de la Loi, 175, Brussels,
Belgium
Tel: 32-2-281-4966
Fax: 32-2-281-7928
philip.landon@consilium.eu.int

BELGIUM – BELGIQUE - BÉLGICA

Chantal Rettigner
Veterinary Expert
DG Control Policy
Federal Agency for the Safety of the Food Chain
WTCIII Boulevard Simon Bolivar 30, B-1000 Brussels
Belgium
Tel: +32 (0)2 208 38 18
Fax: + 32 (0)2 208 38 66
chantal.rettigner@afsca.be

Edith Hoc
Veterinary Officer
Federal Public Service
Health, Food Chain Safety and Environment
Eurostation Bloc II, 7th floor
Place Victor Horta 40, bte 10
1060 Brussels
Belgium
Tel: 32 2 524 73 15
Fax: 32 2 524 73 49
Edith.hoc@health.fgov.be

BRAZIL – BRÉSIL - BRASIL

Ricardo Rego Pamplona
Regulatory Veterinary Drugs Specialist
Ministry of Agriculture, Livestock and Supply
Esplanada Dos Ministérios Bl. "D" – Annex 447-A
Brasília – DF Cep: 70043-900
Brazil
Tel: 55-61-3218 2704
Fax: 55-61-3218 2707
rpamplona@agricultura.gov.br

Lucas Medeiros Dantas
Office of Food Science and Technology Actions Manager
National Health Surveillance Agency - Ministry of Health
SPEN 511, Bloco A, Edifício Bittar II
Brasília – DF CEP: 70541-070
Brasil
Tel: 55-61-3448-6284
Fax: 55-61-3448-6274
gacta@anvisa.gov.br

Maria Angélica Ribeiro de Oliveira
Regulatory Feed Additive Specialist
Ministry of Agriculture, Livestock and Supply
Esplanada dos Ministérios Bl. "D"
Annex 443-A
Brasília – DF Cep: 70043-900
Brazil
Tel: 55-61-3218 2438
Fax: 55-61-3218 2727
ribeiro@agricultura.gov.br

Lígia Lindner Schreiner
Regulatory Health Surveillance Specialist
National Health Surveillance Agency - Ministry of Health
Sepn 511, Bloco A, Edifício Bittar II
Brasília – DF Cep: 70541-070
Brazil
Tel: 55-61-3448-6284-6286
Fax: 55-61-3448-6274
gacta@anvisa.gov.br

Leandro Diamantino Feijó
Residues Coordination- Dipoa/Mapa
Ministry of Agriculture, Livestock and Food Supply- Mapa
Departament of Inspection of Products of Animal Origin- Dipoa
(Esplanada dos Ministérios, Bloco D, Edifício Anexo, sala, 412-a
Brasília – DF Cep: 70043-900
Brazil
Tel: 55-61-32245907
Fax: 55-61-32182672
feijo@agricultura.gov.br

Alexandre Pontes
Codex Manager - Mapa
Ministry of Agriculture, Livestock and Food Supply
Esplanada Dos Ministerios Bloco D Sala 347
Brasília – DF Cep: 70.043-900
Brazil
Tel: 55-61-32182308
Fax: 55-61-32254738
apontes@agricultura.gov.br

João Palermo-Neto
Professor of Pharmacology and Toxicology
University of São Paulo
School of Veterinary Medicine
Av. Prof. Dr. Orlando Marques de Paiva, 87 – Cep 05340-000 São Paulo, SP.
Brazil
Tel: 55-11-3091-7957
Fax: 55-11-3091-7829
jpalermo@usp.br

Cesar Azevedo Lopes
Dvm - Technical & Regulatory Director – Sindan
Sindan – Union of Animal Health Products Manufacturers
Rua do Rocio 313 - Cj 91
04552-000 – Sao Paulo – SP
Brazil
Tel: 55-11-6472-4420
Fax 55-11-6472-4455
cesar.lopes@pahc.com

Clea Camargo
Regulatory Manager
Abiquif-Brazilian Association for Pharmaco-Chemicals
Av. Morumbi, 8264
São Paulo – SP
Brazil
04703-002
Tel: 55-11-21446849
Fax: 55-11- 21446198
camargo_clea@lilly.com

Jean Carlo Cury Manfredini
Foreign Trade Adviser
Brazilian Chicken Producers and Exporters Association – Abef
Av. Brigadeiro Faria Lima, 1912, 12° Floor – Room 12-A
Zip: 01452922 – São Paulo – SP/Brazil
Brazil
Tel: 55-11-38127666
Fax: 55-11-30328895
jean@abef.com.br

Milson Peneira
Director
SINDAN-Union of Animal Health Products Manufacturers
Rua Rocio 313 conj. 91
Vila Olimpia
Sao Paulo 04552-000
Brazil
Tel: 55 11 30 444749
Fax: 55 11 30 444 212
diretor@sindan.org.br

Márcio Caparroz Lopes Pinheiro
Technical Manager
Abiec – Brazilian Beef Export Industries Association
Av. Brigadeiro Faria Lima, 1912
São Paulo – SP Cep: 01451 001 14°
Brazil
Tel: 55-11-3813-1277
Fax: 55-11-3032-5997
marcio@abiec.com.br

CANADA - CANADÁ

Paul Dick
Chair, Canadian Animal Health Institute (CAHI) Drug Committee
Canadian Animal Health Institute
160 Research Lane, Suite 102
Guelph, Ontario N1G 5B2
Canada
Tel: 519-821-0277
Fax: 519-821-7831
p.dick@lilly.com

Yves Babin
Chemist
DLEAA-MAPAQ
2700 Einstein, Room C.2.105
Québec City (PQ) G1P 3W8
Canada
Tel: 418-266-4440 ext. 215
Fax: 418-266-5438
yves.babin@mapaq.gouv.qc.ca

Joe Boison
Senior Research Scientist
CFIA Saskatoon Laboratory
Centre for Veterinary Drug Residues
116 Veterinary Road
Saskatoon, Saskatchewan S7N 2R3
Canada
Tel: (306) 975-5358
Fax: (306) 975-5711
jboison@inspection.gc.ca

Dennis Lein
Senior Advisor, Food Regulatory Program
Bureau of Food Regulatory, International and Interagency Affairs, Food Directorate
Health Products and Food Branch, Health Canada, Building #7
Tunney's Pasture, Ottawa K1A0L2
Canada
Tel: 613-957-1751
Fax: 613-941-3537
Dennis_Lein@hc-sc.gc.ca

James Daniel MacNeil
Head, Centre For Veterinary Drug Residues
Canadian Food Inspection Agency
Saskatoon Laboratory
116 Veterinary Road
Saskatoon, Saskatchewan S7N 2R3
Canada
Tel: 306-975-5347
Fax: 306-975-5711
jmacneil@inspection.gc.ca

Jean Szkotnicki
President
Canadian Animal Health Institute
160 Research Lane, Suite 102
Guelph, Ontario N1G 5B2
Canada
Tel: 519-763-7777
Fax: 519-763-7407
cahi@cahi-icsa.ca

Arnost Vilim
Team Leader – Metabolism and Residue Chemistry Team
Veterinary Drugs Directorate – Health Canada
11 Holland Ave., Suite 14
Ottawa, Ottawa K1A 0K9
Canada
Tel: (613) 957-3880
Fax: (613) 957-3861
Arnost_Vilim@hc-sc.gc.ca

CHINA - CHINE

Qiyi Huang
Professor
China Institute of Veterinary Drug Control
No. 8 Zhongguancun South Street
Beijing
China
Tel: (86)-10-62150572
Fax: (86)-10-62150639
hqiyi@sohu.com
huangqiyi@ivdc.gov.cn

Yinliang Wu
Engineer
Quality Control and Inspection Center for Domestic Animal Products of MOA, P.R.China
No.20 Maizidian Street, Chaoyang District Beijing, 100026
China
Tel: (86) 10-64194682
Fax: (86) 10-64194681
wupaddyfield@tom.com

Wing Ka Au
Veterinary Office
Food and Environmental Hygiene Department
43/F., Queensway Government Offices
66 Queensway
Hong Kong
China
Tel: 852 2867 5429
Fax: 852 2521 8067
wkau@fehd.gov.hk

COSTA RICA

Benigno Alpízar
Jefe de Registro de Medicamentos Veterinarios
Dirección de Salud Animal, Ministerio de Agricultura y Ganadería
Barreal de Heredia
Costa Rica
Tel: (506) 260-8300 Extensión 2069
Fax: (506) 260-5483
balpizar@protecnet.go.cr

José Luis Rojas Martínez
Jefe Sección de Toxicología
Dirección de Salud Animal, Ministerio de Agricultura y Ganadería
Barreal de Heredia
Costa Rica
Tel: (506) 260-8300 Extensión 2177
Fax: (506) 260-5483
jrojas@protecnet.go.cr

CROATIA-CROATIE-CROACIA

Visnja Papac
Ministry of Agriculture, Forestry and Water Management
Veterinary Department
Ulica grada Vukovara 78
10000 Zagreb
Croatia
Tel: ++385 1 610 9 546
Fax: ++385 1 610 9 202
visnja.papac@mps.hr

CZECH REPUBLIC

Alfred Hera
General Manager
Institute for State Control of Veterinary Medicaments
62100 Brno,Hudcova str. 56A;
Czech Republic
Tel: 00420 541 212380
Mobile: 00420 602 487 743
Fax: 00420 541210026
Hera@uskvbl.cz

DENMARK – DANEMARK - DINAMARCA

Kim Petersen
Master of Science
Danish Veterinary and Food Administration
Mørkhøj Bygade 19
2960 Søborg
Denmark
Tel: 045 3395 6203
kimp@fvst.dk

EGYPT-ÉGYPTE-EGYPTO

Hussein Mansour
Head of Delegation
Agricultural Minister Plenipotentiary and Head of the Agricultural Office
Embassy of the Arab Republic of Egypt
3521 International Court, NW
Washington, DC 20008
United States
Tel: 1-202-966-2080
Fax: 1-202-895-5493
hmkmansour@aol.com
agegypt@aol.com

Farouk Abd El-Wahab Badr
Director General
General Department for Services and Extension
General Authority for Veterinary Services
Tel: +20 2 337 5692
Fax: +20 2 336 1727

EUROPEAN COMMUNITY (MEMBER ORGANIZATION) - COMMUNAUTÉ EUROPÉENNE (ORGANIZACION MEMBRE) - COMUNIDAD EUROPEA (ORGANIZACIÓN MIEMBRO)

Alain Dehove
Head of Delegation
European Commission
Health and Consumer Protection Directorate-General
B-1049 Brussels
Belgium
Tel: 32-2-295 2538
alain.dehove@ec.europa.eu

Anne Gautrais
European Commission
Directorate-General Enterprise and Industry
Avenue d'Auderghem 45 10/65
B-1049 Brussels
Belgium
Tel: 32-2-295 2984
Fax: 32-2-299 8046
anne.gautrais@ec.europa.eu

Gudrun Gallhoff
European Commission
Health and Consumer Protection Directorate-General
B-1049 Brussels
Belgium
Tel: 32-2-296 71 28
gudrun.gallhoff@ec.europa.eu

Kornelia Grein
Head of Section
Safety of Veterinary Medicinal Products
European Medicines Agency
7, Westferry Circus, Canary Wharf
London E14 4HB,
United Kingdom
Tel: 44 207 418 8400
(direct 44 207 418 8432)
Fax: 44 207 418 8447
kornelia.grein@emea.eu.int

FINLAND - FINLANDE - FINLANDIA

Leena Anneli Räsänen
Veterinary Counselor
Ministry of Agriculture and Forestry
Department of Food and Health
P. O. Box 30
FIN-00023 Government
Finland
Tel: 358-9-1605 2207
Fax: 358-9-1605 3338
leena.rasanen@mmm.fi

FRANCE - FRANCIA

Gérard Moulin
Head of the Marketing Authorisation Department
AFSSA / ANMV
La Haute Marche
BP 90203 – 35302 Fougeres
France
Tel: 33 2 99 94 78 58
Fax: 33 2 99 94 78 64
g.moulin@anmv.afssa.fr

Pascal Audebert
Point de Contact du Codex Alimentarius en France
Premier Ministre – Secretariat General des Affaires Europeennes
2, Boulevard Diderot
75572 Paris Cedex 12
France
Tel: 33 1 44 87 16 03
Fax: 33 1 44 87 16 04
sgae-codex-fr@sgae.gouv.fr
pascal.audebert@sgae.gouv.fr

Georges Monsallier
Honorary President
S I M V
11 rue des Messageries, 75010
Paris
France
Tel: 33 6 61 87 22 51
Fax: 33 2 23 20 75 89
georges.monsallier@wanadoo.fr

Jean-Pierre Orand
Ministry of Agriculture General Directorate for Food
251 rue de Vaugirard 75732
Paris Cedex 15
France
Tel: 33149555843
Fax: 33149554022
jean-pierre.orand@agriculture.gouv.fr

GERMANY – ALLEMAGNE - ALEMANIA

Silva Undine Buettner-Peter
Head of Delegation
Bundesministerium für Ernährung, Landwirtschaft und Verbraucherschutz
(Federal Ministry of Food, Agriculture and Consumer Protection)
Rochusstraße 1
D-53123 Bonn
Germany
Tel.: +49(0)228-529 4644
Fax: +49(0)228-529 4946
326@bmelv.bund.de

Reinhard Kroker
Abteilungsleiter
Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
(Federal Office of Consumer Protection and Food Safety)
Dienststelle Berlin
Diedersdorfer Weg 1
D-12277 Berlin
Germany
Tel.: +49(0)30-412-2364
Fax: +49(0)30-412-2965
reinhard.kroker@bvl.bund.de

Ludwig Klostermann
Bayer Health Care
Animal Health Division
Policy and Issues Management
Gebäude 4845
D-51368 Leverkusen
Germany
Tel: +49(0)2173 383-861
Fax: +49(0)2173 383-539
Ludwig.Klostermann.@bayerhealthcare.com

Martin Schneidereit
Geschäftsführer
Bundesverband für Tiergesundheit e.V.
Aennchenplatz 6
D-53173 Bonn
Germany
Tel.: +49(0)228-318 296
Fax: +49(0)228-318 298
m.schneidereit@bft-online.de

Thomas Heberer
Federal Institute for Risk Assessment
(BfR), Dept. for Residues of Medicinal Products
Thielallee 88-92
14195 Berlin
Germany
Tel: +49(0)30 8412 4263
Fax: +49(0)30 8412 4741
t.heberer@bfr.bund.de

GREECE – GRÈCE - GRECIA

Dimitrios Milionis
Technical Manager
Greek Ministry of Rural Development and Food
Neapoleos 25
15310, Agia Paraskevi
Athens, 15310
Greece
Tel: 003 210-0013899
Fax: 003 210-6012594
kkia@otenet.gr
cyyia@otenet.gr

HUNGARY – HONGRIE - HUNGRÍA

Lorena Kovacsics
Chair of Hungarian CAC CCRVDF
National Food Investigation Institute
1095. Mester u. 81
BUDAPEST
Hungary
Tel: 00 36 1 456 3021
Fax: 00 36 1 215 6858
kovacsil@oai.hu

Miklós dr Süth
Secretary of Hungarian CAC CCRVDF
Ministry of Agriculture and Rural Development
Head of Animal Health Division
Kossuth Lajos tér 11
H-1055 Budapest,
Hungary
Tel: 00 36 1 301 413
Fax: 00 36 1 301 4822
suthm@oai.hu
suthm@fum.hu

INDONESIA - INDONÉSIE

Edy Sutrisno
Head of Delegation of Indonesia
Calle Julio Verne 27
Colonia Polanco
Mexico City 11560
Mexico
Tel: +52 55 5280 6363
Fax: +52 55 5280 7062
edysutrisno@yahoo.com

Tony Unandar
Elanco Animal Health Indonesia
Mid Plaza 2, Lt. 14
Jakarta, 10220
Indonesia
Tel: (62-21) 570 7725
Fax: (62-21) 570 7716
unandar_tony@lilly.com

Sri Wahyuni
Indonesian Embassy in Mexico City
Calle Julio Verne 27
Colonia Polanco
Mexico City 11560
Mexico
Tel: +52 55 5280 6363
Fax: +52 55 5280 7062
iyoeniyoen@gmail.com

IRELAND – IRLANDE - IRLANDA

Ciaran O'Sullivan
Veterinary Officer
Food Safety Authority of Ireland
Abbey Court
Lower Abbey Street
Dublin 1
Ireland
Tel: 01 8171361
Fax: 01 8171261
cosullivan@fsai.ie

Paul Rafter
Superintending Veterinary Inspector
Department of Agriculture and Food
Central Meat Control Laboratory
Backweston Campus
Celbridge, Co. Kildare
Ireland
Tel: 01 6157350
Fax: 01 6157361
Paul.Rafter@agriculture.gov.ie

JAPAN – JAPON - JAPÓN

Katsuaki Sugiura
Head of Delegation
Director, Animal Products Safety Division
MAFF
1-2-1 Kasumigaseki, Chiyoda-ku
Tokyo 100-8950
Japan
Tel: 81 3 3502 8206
Fax: 81 3 3502 8275
katsuaki_sugiura@nm.maff.go.jp

Koji Nishizawa
Technical Advisor
1-1-13, Hanabatake Tsukuba
City, Ibaragi 300-3261
Japan
Tel: 029-879-0024
Fax: 029-879-0024
koji_nishizawa@meiji.co.jp

Yuuko Endoh
Ministry of Agriculture Forestry and Fisheries
1-2-1 Kasumigaseki Chiyoda-ku
Tokyo 100-8950
Japan
Tel: 81 3 3502 8097
Fax: 81-3-3502-8275
Yuuko_endo@nm.maff.go.jp

Koji Uchida
Technical Advisor
5-47-9-304 Hirai Edogawa-ku
Tokio
Japan
Tel: 81-3-5309-7276
Fax: 81-3-5309-9875
koji.uchida@pfizer.com

Takuya Kondo
Technical Officer
Ministry of Health, Labor and Welfare
1-2-2 Kasumigaseki Chiyoda-ku
Tokyo 100-8916
Japan
Tel: 81-3-5253-1111
Fax: 81 3 3501 4868
kondo-takuya@mhlw.go.jp

Hideyuki Hirano
Official
Food Safety Commission Secretariat
Prudential Tower 6F 2-13-10
Nagata-cho, Chiyoda-ku
Tokyo 100-8989
Japan
Tel: 81 3 5251 9149
Fax: 81 3 3591 2236
hideyuki.hirano@cao.go.jp

KENYA

James Ngandu Karitu
Assistant Director of Veterinary Services
Department of Veterinary Services
Veterinary Research Laboratory
P.O. Box 00625 Kangemi
Nairobi
Kenya
Tel: 254 20 631289
Fax: 254 20 631790
ngandukaritu@yahoo.com.or
jkaritu@dvskabete.go.ke

LITHUANIA

Arturas Bagotyrius
Deputy Director
State Food and Veterinary Service
Siesiku 19
LT-07170 Vilnius
Lithuania
Tel: 370 5 249 16 55
Fax: 370 6 982 11 51
abagotyrius@vet.lt

MALAYSIA – MALAISIE - MALASIA

Zaliha Abdullah
Deputy Director
Veterinary Public Health Section
Department of Veterinary Services Malaysia
Wisma Tani, Podium, 1A
Block 4G1, Precint 4
Federal Government Administration Centre
62630 Putrajaya
Malaysia
Tel: 603-8870 2019
Fax: 603-8888 5755
zaliha@jph.gov.my

Hamdan Jaafar
Section Head – Laboratory Services
Department of Fisheries Malaysia
Level 3, Block 4G2, Wisma Tani, Precinct 4
Federal Government Administration Centre
62628 Putrajaya
Malaysia
Tel: 603-8870 4000
Fax: 603-8889 1055
hamdanj@yahoo.com

MEXICO – MEXIQUE - MÉXICO

Fernando Rivera Espinoza
Head of Delegation
Departamento de Control y Regulación de Empresas y Productos
SAGARPA – SENASICA
Municipio Libre # 377, Piso 7 ala "A"
Col. Santa Cruz Atoyac, Del. Benito Juárez, C.P. 03310
México D.F.
Mexico
Tel: (52) 55 9183 1000 Ext: 33955
Fax: (52) 55 9183 1000 Ext: 33945
ssi.dgsa@senasica.sagarpa.gob.mx

Juan Manuel Carrillo García
Vocal
Asociación Nacional de la Industria Farmacéutica Veterinaria
Gabriel Castaños #85
Col. Arcos Vallarta, C.P. 44130
Boadalajara, JAL
Mexico
Tel: (52) 33 36 15 11 18
direccion@haluet.com

Bertha Iliana Giner Chávez
Gerente de Regulatorio e Investigación
Elanco Animal Health Latinoamérica
Circuito del Patrón 50
Col. Residencial La Hacienda Coahuila
Torreón, Coahuila, C.P. 27276
Mexico
Tel: (52) 871 731 0026
Fax: (52) 871 731 0026
giner_bertha@elanco.com
GINER_BERTHA@Lilly.com

Ofelia Flores Hernández
Subdirectora de Constatación
SAGARPA – SENASICA
Carretera Federal Cuernavaca-Cuautla, Col.
No. 8534 Progreso, C.P. 62550
Jiutepec, Morelos
México
Tel: (52) 777 319 5835
Fax: (52) 777 319 0202
cons.cen@senasica.sagarpa.gob.mx

Hugo Fragoso Sánchez
Director del Centro Nacional de Servicios de Constatación de Salud Animal
SAGARPA – SENASICA
Carretera Federal Cuernavaca-Cuautla No 8534 Col. Progreso, C.P. 62500
Jiutepec, Morelos
Mexico
Tel: (52) 777 319 5835
Fax: (52) 777 319 0202
dir.cen@senasica.sagarpa.gob.mx

Miguel Ángel García
Subdirector de Inocuidad Pecuaria
SAGARPA - SENASICA
Guillermo Pérez Valenzuela No. 127 P.B.
Col. Del Carmen Coyoacán, C.P. 04100
México, D.F.
Mexico
Tel: (52) 55 5658 2828
Fax: (52) 55 5659 3478
ino.mzn@senasica.sagarpa.gob.mx

Juan Carlos Gómez Araujo
Auditor de Establecimientos TIF
SAGARPA/SENASICA/DGIAAP
Guillermo Pérez Valenzuela No 127
Col. Del Carmen Coyoacán, C.P. 04100
México, D.F.
Mexico
Tel: (52) 55 56 59 12 06 Ext. 229
Fax: (52) 55 56 59 10 91 Ext 229
jcgomez@senasica.sagarpa.gob.mx

Juan Carlos Guzmán Ruiz
Gerente de Registros
Manager Register
Lapisa, S.A. de C.V.
Km. 5.5 Carretera La Piedad Guadalajara, C.P. 59300
La Piedad, Michoacán
México
Tel.: (52) 352 52 6 13 00
Fax: (52) 352 52 5 81 88
jcgr@lapisa.com

Mario Pérez Leyton
Director Ejecutivo – INFARVET
Industria Farmacéutica Veterinaria – CANIFARMA
Av. Cuauhtémoc 1481, Col. Santa Cruz Atoyac Del.
Benito Juárez, C.P. 03310
México D.F.
Mexico
Tel: (52) 55 688 96 16
Fax: (52) 55 601 25 03
infarvet@mx.inter.net

Alejandra Reyes Saucedo
Jefa del Departamento de Integración de Lácteos
Coordinación General de Ganadería SAGARPA
Municipio Libre No. 377, Piso 2-A
Col. Santa Cruz Atoyac
Del. Benito Juárez, C.P. 03310
México, D.F.
Mexico
Tel: (52) 9183 1000 Ext. 33219
Fax: (52) 9183 1000 Ext. 33229
areyes.cgg@sagarpa.gob.mx

Francisco Romo López
Vicepresidente – INFARVET
Industria Farmacéutica Veterinaria – CANIFARMA
Av. Cuauhtémoc 1481, Col. Santa Cruz Atoyac, Del.
Benito Juárez
México D.F., C.P. 03310
Mexico
Tel: (52) 55 688 96 16
Fax: (52) 55 601 25 03
infarvet@mx.inter.net,
romo@lapisa.com

Margarita Salazar Juárez
Gerente Administrativo
Parfarm, S.A.
Aragon No. 25
Col. Alamos
Mexico, D.F.
Mexico
Tel: (52) 55-38-00-40
Fax: (52) 55-38-44-29
msalazar@parfarm.com

Raúl Vázquez Martínez
Presidente INFARVET
Industria Farmacéutica Veterinaria – CANIFARMA
Av. Cuauhtémoc 1481, Col. Santa Cruz Atoyac, Del.
Benito Juárez, C.P. 03310
México D.F.
Mexico
Tel: (52) 55 688 96 16
Fax: (52) 55 601 25 03
infarvet@mx.inter.net
raul.vazquez.rv1@bayer.com.mx

Constancio Velásquez Coronel
Gerente Técnico y De Ventas
Parfarm, S.A.
Aragon No. 25
Col. Alamos
México, D.F.
Mexico
Tel: (52) 55-38-00-40
Fax: (52) 55-38-44-29
cvelazquez@parfarm.com

THE NETHERLANDS – PAYS-BAS – PAÍSES BAJOS

Gijsbertus Theodorus Johannes Maria Theunissen
Head of Delegation
Ministry of Agriculture, Nature and Food Quality
Bezuidenhoudseweg 73
2500 EK, Den Haag
The Netherlands
Tel: 31 70 378 4594
Fax: 31 70 378 6177
Gijs.Theunissen@minlnv.nl

Arie Ottevanger
Policy Coordinator Veterinary Food Safety Policy
Ministry of Health, Welfare and Sport
P.O. Box 20350
2500 EJ Den Haag
The Netherlands
Tel: 31 70 340 68 86
Fax: 31 70 340 55 54
a.ottevanger@minvws.nl

Leendert A. van Ginkel
Head Laboratory for Food and Residue Analyses (RIVM)
RIVM – National Institute of Public Health and the Environment
P.O. Box 1
NL 3720 BA Bilthoven
The Netherlands
Tel: 31 30 2742747
Fax: 31 30 2744403
Leen.van.ginkel@rivm.nl

NEW ZEALAND – NOUVELLE-ZÉLADE – NUEVA ZELANDIA

Bill Jolly
Deputy Director (Export Standards)
New Zealand Food Safety Authority
PO Box 2835
Wellington
New Zealand
Tel: 64 4 463 2621
Fax: 64 4 463 2643
bill.jolly@nzfsa.govt.nz

Neil Kennington
Senior Advisor
New Zealand Food Safety Authority
PO Box 2835
Wellington
New Zealand
Tel: 64 4 463 2555
Fax: 64 4 463 2566
neil.kennington@nzfsa.govt.nz

NORWAY – NORVÈGE - NORUEGA

Inger Halle
Advisor, Norwegian Food Safety Authority
Section for Contaminants and Cosmetics
Villevalsveien 76
Oslo
Norway
Tel: 47 23 21 6852
inger.halle@mattilsynet.no

Tone Norman Asp
Section of Food Safety
Norwegian School of Veterinary Science
P.O. Box 8146 Dep.
No-0033 Oslo
Norway
Tel: 47 2296 4832
Fax: 47 22 96 4850
tone.asp@veths.no

PHILIPPINES - FILIPINAS

Marvin Vicente
Supervising Meat Control Officer and Head Laboratory Services Division
Department of Agriculture—National Meat Inspection Service
Visayas Ave.Diliman, Quezon City 1100
Philippines
Tel: 632 924 3119/ 924-7971
Fax: 632 924 7973
vicentemarvin@yahoo.com

REPUBLIC OF KOREA – RÉPUBLIQUE DE CORÉE – REPÚBLICA DE COREA

Jeong Sang-Hee
Head of Delegation
Deputy Director
Toxicology and Biochemistry Division
National Veterinary Research and Quarantine Service
Ministry of Agriculture and Forestry
480, Anyang-6-dong, Anyang City,
430-016
Korea
Tel: 82-31-467-1837
Fax: 82-31-467-1845
jeongsh@nvrqs.go.kr

Jong Sung Park
Deputy Director
Ministry of Health and Welfare
Food Policy Team, Bureau of Health Policy
Anyang Construction Tower 10F, 1112-1 Bisandong,
Dongan-ku, Anyang-si,
Gyeonggi-do
Korea
Tel: 82 31 440-9115/8
Fax: 82-31-440-9119
pjsung@mohw.go.kr

Sung Myung Bae
Food Management Team, Kyung-In Regional
Korea Food and Drug Administration
#120, Juan-1-dong
Nam-gu, Incheon, Kyung-ki
Korea
Tel: 82-32-480-3332
Fax: 82-32-442-4619
smbae_23@kfda.go.kr

Jiyoon Jeong
Scientific Officer
Residues and Chemical Team
Department of Food Evaluation
Korea Food and Drug Administration
5, Nokbun Dong, Eunpyungu, Seoul, 122-407
Korea
Tel: 82-2-380-1675
Fax: 82-2-380-1378
stopyoon@kfda.go.kr

Mijung Park
Researcher
National Fisheries Product Quality Inspection Service
912-7, Joongsan-dong, Ilsan-donggu,
Koyang-City, Gyeonggi-do
Korea
Tel: 82-31-976-3024
Fax: 82-31-976-6391
parkmj@momaf.go.kr

Boram Kim
Scientific Officer
Risk Information Team
The Bureau for Risk Management
Korea Food and Drug Administration
5 Nokbun-dong, Eunpyung-gu
Seoul 122-704
Korea
Tel: 82 2 380 1366, 1382
Fax: 82 2 385 3761
boram@kfda.go.kr

SLOVENIA – SLOVÉNIE - ESLOVENIA

Maja Kokalj
Veterinary Administration of the Republic of Slovenia
Ministry of Agriculture, Forestry and Food
Parmova 53
Ljubljana SI
Slovenia
Tel: 38 61 3001 300
Fax: 38 61 300 1356
maja.kokalj@gov.si

SOUTH AFRICA – AFRIQUE DU SUD - SUDÁFRICA

Mmalencoe Moroe-Rulashe
Head of Delegation
Technical Advisor: Stock Remedies
Directorate: Food Safety and Quality Assurance
Department of Agriculture
Private Bag X343
Pretoria, 0001
South Africa
Tel: +27-12 319 6671
Fax: +27-12 319 6765
MmalencoeM@nda.agric.za

Richard Burroughs
Chief State Veterinarian: Import Export Policy Unit
Directorate: Animal Health
Department of Agriculture
Private Bag X138
Pretoria, 0001
South Africa
Tel: +27-12 319 7420
Fax: +27-12 319 7491
RichardBu@nda.agric.za

Tlou Mokoele
Principal Medicines Registration Officer
Directorate: Medicines Evaluation and Research
Department of Health
Private Bag X828
Pretoria, 0001
South Africa
Tel: +27-12 312 0301
Fax: +27-12 312 3104
mokoet@health.gov.za

SPAIN – ESPAGNE – ESPAÑA

Santiago Gutiérrez del Arroyo
Head of Delegation
Agencia Española Seguridad Alimentaria
Ministerio Sanidad y Consumo
Alcala No 56
Madrid 28014
Spain
Tel: 34 91 3 380 620
Fax: 34 91 3 38 0169
sgutierrez@msc.es

Gema Cortes Ruiz
Senior Assessor of Veterinary Medicines
Agencia del Medicamento Ministerio Sanidad y Consumo
Alcala 56
Madrid 28014
Spain
Tel: 34 91 8225431
Fax: 34 91 8225443
gcortes@agemed.es

SWEDEN – SUÈDE - SUECIA

Tor Bergman
Head of Delegation
Dep Chief Veterinary Officer (CVO) PH National Food Administration, Box 622
SE- 751 26 Uppsala
Sweden
Tel: 46 18 175587
Fax: 46 18 175310
tor.bergman@slv.se

Bitte Aspenström – Fagerlund
Toxicologist
National Food Administration
Box 622
SE-751 26 Uppsala
Sweden
Tel: 46 18 171446
Fax: 46 18 105848
bfas@slv.se

Hakan Johnsson
Senior scientist
National Food Administration
Box 622
SE-751 26 Uppsala
Sweden
Tel: 46 18 17 57 05
Fax: 46 18 17 55 29
hajo@slv.se

SWITZERLAND – SUISSE - SUIZA

Ursula Witschi
Dr. Med. Vet, Scientific Employee
Swiss Federal Office of Public Health
CH – 3003 Bern
Switzerland
Tel: 41 31 323 44 31
Fax: 41 31 322 95 74
ursula.witschi@bag.admin.ch

THAILAND – THAÏLANDE - TAILANDIA

Nantana Posanacharoen
Senior Veterinary Officer
National Bureau of Agricultural Commodity and Food Standards
Ministry of Agriculture and Cooperatives
Rajadamnoon Nok, Avenue
Bangkok, 10200
Thailand
Tel: 66 2 283 1600
Fax: 66 2 280 3899

Sujittra Phongvivat
Veterinary Drug Residue Analysis Section
Veterinary Public Health Laboratory
Bureau of Quality Control of Livestock Products
Department of Livestock Development,
Tiwanont Rd., Patumtanee 12000
Thailand
Tel: 66 2 967 9705
Fax: 66 2 963 9217
sujittrap@dld.go.th
sujittra_dvm@yahoo.com

Sasi Jaroenpoj
Head of Food Safety Policy and Planning Section
Bureau of System Development and Standard Certified of Livestock Products
Department of Livestock Development
Phayathoi Rd. Ratchtaevee
Bangkok 10400
Thailand
Tel: 66 2 653 4444 Ext. 3142
Fax: 66 2 653 4917
sasijaroenpoj@yahoo.com

Orawan Kaewprakaisangkul
Director, Lab Services Dept.
Industrial Development Foundation National Food Institute
2008 Soi Charansanitwong 40 Charansanitwong Road
Bangyeekhan Bangphlad
Bangkok 10700
Thailand
Tel: 66 2 886 8088 Ext. 500
Fax: 66 2 886 8088 Ext. 588
orawan@nfi.or.th

Boonpeng Santiwattanatam
Vice-Chairman, Food Processing Industry Club
The Federation of Thai Industries
Queen Sirikit National Convention Center
Zone, 4th Floor, 60 New Rachadapisek
Klongtoey, Bangkok 10110
Thailand
Tel: 66 2 638 2226
Fax: 66 2 63 0725
boonpeng@cpf.co.th

UNITED KINGDOM – ROYAUME-UNI – REINO UNIDO

John FitzGerald
Head of Delegation
Policy Director
VMD
Woodham Lane
New Haw
Addlestone KT15 3LS
United Kingdom
Tel: 44 1932 338303
Fax: 44 1532 338348
j.fitzgerald@vmd.defra.gsi.gov.uk

Jack Kay
R&D and Science Policy Team Leader
Veterinary Medicines Directorate
Woodham Lane, New Haw,
Addlestone, KT15 3LS
United Kingdom
Tel: 44 1932 338323
Fax: 44 1932 336618
j.kay@vmd.defra.gsi.gov.uk

UNITED STATES OF AMERICA – ÉTATS UNIS D'AMÉRIQUE – ESTADOS UNIDOS DE AMÈRICA

Steven Vaughn
Head of Delegation
Director, Office of New Animal Drug Evaluation
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
7500 Standish Place, MPN2
Rockville, MD 20855
United States
Tel**:** 301-827-1796
Fax: 301-594-2297
Steven.Vaughn@fda.hhs.gov

Bernadette Dunham
Deputy Director, Office of New Animal Drug Evaluation
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
7500 Standish Place, MPN2
Rockville, MD 20855
United States
Tel: 301-827-0204
Fax: 301-594-2297
Bernadette.Dunham@fda.hhs.gov

Kevin Greenlees
Toxicologist
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
7500 Standish Place, MPN2
Rockville, MD 20855
United States
Tel: 301-827-6977
Fax: 301-594-2298
Kevin.Greenlees@fda.hhs.gov

Steven Brynes
Chemist
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
7500 Standish Place, MPN2
Rockville, MD 20855
United States
Tel: 301-827-6975
Fax: 301-594-2298
Steven.Brynes@fda.hhs.gov

Lynn Freidlander
Chemist
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
7500 Standish Place, MPN2
Rockville, MD 20855
United States
Tel: 301-827-6985
Fax: 301-594-2298
Lynn.Friedlander@fda.hhs.gov

Philip Kijak
Chemist
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of Research
8401 Muirkirk Road
Laurel, MD 20708
United States
Tel: 301-210-4589
Fax: 301-210-4653
Philip.Kijak@fda.hhs.gov

Valerie Reeves
Chemist
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
7500 Standish Place, MPN2
Rockville, MD 20855
United States
Telephone: 301-827-6973
Fax: 301-594-2298
Valerie.Reeves@fda.hhs.gov

Richard Coulter
Vice President, Scientific and Regulatory Affairs
Phibro Animal Health
65 Challenger Road
Ridgefield Park, NJ 07660
United States
Tel: 201-329-7374
Fax: 201-329-7042
Richard.Coulter@pahc.com

Paul Duquette
Director, Global Regulatory Affairs
Phibro Animal Health
65 Challenger Road
Ridgefield Park, NJ 07660
United States
Tel: 201-329-7375
Fax: 201-329-7042
Paul.Duquette@pahc.com

Bruce Martin
Director, Regulatory Affairs
Bayer Health Care LLC
Animal Health
P.O. Box 390
Shawnee Mission, KS 66201-0390
United States
Tel: 913-268-2779
Fax: 913-268-2075
Bruce.Martin.B@bayer.com

Larry Stobbs
Director, Regulatory Affairs
Elanco Animal Health
2001 W. Main Street
P.O. Box 708
Greenfield, IN 46140
United States
Tel: 317-277-4087
Fax: 317-277-4962
L.A.Stobbs@lilly.com

Sondra Flick
Director, Government and Industry Affairs
Alpharma Animal Health
One Executive Drive
Fort Lee, NJ 07024
United States
Tel: 201-228-5074
Fax: 201-947-0912
Sandy.Flick@alpharma.com

Elizabeth Curry-Galvin
Interim Director, Scientific Activities Division
American Veterinary Medical Association
1931 Meacham Road
Suite 100
Schaumburg, IL 60173-4360
United States
Tel: 847-925-8070
Fax: 847-925-9329
Egalvin@avma.org

Richard Ellis
RLE Consult
8081 Wacobee Drive
Myrtle Beach, SC 29579-5229
United States
Tel: 843-903-7380
Fax: 843-903-7380
rle_foodsafety@yahoo.com

Richard Wood
Executive Director
Food Animal Concerns Trust (FACT)
P.O. Box 14599
Chicago, IL 60614
United Status
Tel: 773-525-4952
Fax: 773-525-5226
RRWood@FACT.cc

Raúl Guerrero
Technical Consultant
793 N. Ontare Road
Santa Barbara, CA 93105
United States
guerrero_raul_j@yahoo.com

URUGUAY

Jorge Manuel Alves Suárez
Encargado Inocuidad de la Carne
National Meat Institute (INAC)
Rincón 545
Montevideo
Uruguay
Tel: 598-2 916 0430
Fax: 598-2 915 0875
jalves@inac.gub.uy

INTERNATIONAL GOVERNMENTAL ORGANIZATIONS – ORGANISATIONS GOUVERNAMENTALES INTERNATIONALES - ORGANISACIONES GOUBERNAMENTALES INTERNACIONALES

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO) – ORGANISATION DE NATIONS UNIES POUR L'ALIMENTATION ET L'AGRICULTURE – ORGANIZACION DE LAS NACIONES UNIDAS PARA AGRICULTURA Y LA ALIMENTACION

Annika Wennberg
FAO JECFA Secretary
Nutrition and Consumer Protection Division
Viale della Terme di Caracalla
00100 Rome
Italy
Tel: 39 065 705 3283
Fax: 39 065 705 4593
Annika.Wennberg@fao.org

Norman Bellino
Representante
Organización de las Naciones Unidas para la Agricultura y la Alimentación
Farallón No 130
Col. Jardines del Pedregal C.P. 01900
México, D.F.
Mexico
Tel: (52) 55 5652 4903
Fax: (52) 55 5568 4595
FAO-MX@fao.org

FAO/IAEA JOINT DIVISION

Andrew Cannavan
Head, Agrochemicals Unit
FAO/IAEA Agriculture and Biotechnology Laboratory
A-2444 Seibersdorf
Austria
Tel: (43 1) 2600 28395
Fax: (43 1) 2600 28222
a.cannavan@iaea.org

Alfredo Montes Niño
Cost Free Consultant
Laboratorios Microbioticos s/c/ Ltda
Residues Laboratory
Av. Santa Isabel 2116
Caixa Postal 6175
Campinas Estado de Sao Paulo
CEP 13083-970
Brazil
Tel: 55 19 3289 9690
Fax: 55 19 3289 9690

ORGANISMO INTERNACIONAL REGIONAL DE SANIDAD AGROPECUARIA (OIRSA)

Carlos Roberto Menéndez
Coordinador Regional de Registro de Medicamentos Veterinarios
OIRSA
21 Avenida 3-12 zona 15
Vista Hermosa I
Guatemala City
Guatemala
Tel: 502 2369 5900
Fax: 502 2365 8599
cmenendez@oirsa.org.gt

WORLD HEALTH ORGANIZATION (WHO) – ORGANISATION MONDIALE DE LA SANTE (OMS) - ORGANIZACION MONDIAL DE LA SALUD (OMS)

Angelika Tritscher
WHO JECFA Secretary
International Program on Chemical Safety
World Health Organization
20 Avenue Appia
Ch-1211 Geneva 27
Switzerland
Tel: 41 22 791 35 69
Operator: 41 22 791 21 11
Fax: 41 22 791 48 48
tritschera@who.int

Awa Aidara-Kane
Scientist
Department of Food Safety, Zoonoses and Foodborne Diseases
World Health Organization
20 Avenue Appia
CH 1211 Geneva 27
Switzerland
Tel: 41 22 791 24 03
Fax: 41 22 791 48 93
aidarakanea@who.int

WORLD ORGANIZATION FOR ANIMAL HEALTH (OIE)

Patrick Dehaumont
Director of the OIE Collaborating Centre for Veterinary Medicinal Products
Agence Nationale du Médicament Vétérinaire
B.P. 90203
La Haute Marche, Javené
35302 Fougères Cedex
France
Tel: 33-2 99 94 78 71
Fax: 33-2 99 94 78 99
p.dehaumont@anmv.afssa.fr

INTERNATIONAL NON-GOVERMENTAL ORGANIZATIONS - ORGANISATIONS NON-GOUVERNAMENTALES INTERNATIONALES - ORGANISACIONES INTERNACIONALES NO GOUBERNAMENTALES

CONSUMERS INTERNATIONAL

Steven Roach
Food Safety Program Manager
Food Animal Concerns Trust
P.O. Box 14599
Chicago, IL 60614
United States
Tel: 515-232-2278
Fax: 815-301-1889
saroach@fact.cc

INTERNATIONAL CO-OPERATIVE ALLIANCE

Kazuo Onitake
Head of Unit, Safety Policy Service
Japanese Consumers' Co-operative Union (JCCU)
Co-Op Plaza, 3-29-8
Shibuya, Shibuya-ku
Tokyo, 150-8913
Japan
Tel: 81 3 5778 8109
Fax: 81 3 5778 8002
Kazuo.onitake@jccu.coop

INSTITUTE OF FOOD TECHNOLOGISTS

Randy Huffman
Vice President, Scientific Affairs
American Meat Institute Foundation
1150 Connecticut Ave., N.W., 12th Floor
Washington, D.C. 20036
United States
Tel: 202-587-4233
Fax: 202-587-4300
rhuffman@meatami.com

Rosetta Newsome
Director, Science and Communications
Institute of Food Technologists
World Headquarters
525 Van Buren Street, Suite 1000
Chicago, IL 60607
United States
Tel: 312-782-8424
Fax: 312-782-8348
rlnewsome@ift.org

INTERNATIONAL DAIRY FEDERATION

Robin Condron
Manager Research & Development - Consumer and Market Assurance Division
Dairy Australia
Locked Bag 104
Flinders Lane
Victoria 8009
Australia
Tel: +61 3 9515 0432
Fax: +61 3 9515 0432
RCondron@dairyaustralia.com.au

INTERNATIONAL FEDERATION FOR ANIMAL HEALTH

Peter G.H. Jones
Executive Director
IFAH
Rue Defacqz, 1
1000 Brussels
Belgium
Tel: 32-2-541-0111
Fax: 32-2-541-0119
p.jones@ifahsec.org

Dennis L. Erpelding
Manager
Elanco Government Relations, Public Affairs and Communications
Elanco Animal Health
2001 West Main Street
P.O. Box 708
Greenfield, IN 46140
United States
Tel: 317-276-2721
Fax: 317-433-6353
dle@lilly.com

Katherine Allran
Technical Director
Regulatory Affairs North America
Merial Limited
3239 Satellite Blvd., Bldg. 500
Duluth, GA 30096
United States
Tel: 678-638-3476
Fax: 678-638-3715
katherine.allran@merial.com

Robert Livingston
Director of International Affairs and Regulatory Policy
Animal Health Institute
1325 G Street, NW Suite 700
Washington, DC 20005-3104
United States
Tel: 202-637-2440
Fax: 202-393-1667
rlivingston@ahi.org

David Gottschall
Associate Research Fellow
PFIZER Animal Health
7000 Portage Road
Kalamazoo, MI 49001-0199
United States
Tel: 269-833 2466
Fax: 269-833 3302
gottsd@pfizer.com

Larry Stobbs
Director, Regulatory Affairs
Elanco Animal Health
2001 West Main Street
P.O. Box 708
Greenfield, IN 46140
United States
Tel: 317 277 4087
Fax: 317 277 4962
stobbs_larry_a@lilly.com

SECRETARIAT

CODEX

Annamaria Bruno
Food Standards Officer
Joint FAO/WHO Food Standards Program
Viale delle Terme di Caracalla
00100 Rome
Italy
Tel: 39 06 570 56256
Fax: 39 06 57 0 56 593
annamaria.bruno@fao.org

Noriko Iseki
Senior Food Standards Officer
Joint FAO/WHO Food Standards Program
Viale delle Terme di Caracalla
00100 Rome
Italy
Tel: 39 06 570 53195
Fax: 39 06 570 54593
noriko.iseki@fao.org

MEXICO

Beatriz Martínez Reding
SAGARPA – SENASICA
Municipio Libre # 377, Piso 7 ala "A"
Col. Santa Cruz Atoyac, Del. Benito Juárez, C.P. 03310
México D.F.
Mexico
Tel: (52) 55 91 83 1000
Fax: (52) 55 91 83 1000 Ext. 33945
dgsv.div@senasica.sagarpa.gob.mx

Víctor Hugo Rodríguez Díaz
SAGARPA – SENASICA
Municipio Libre # 377, Piso 7 ala "A"
Col. Santa Cruz Atoyac, Del. Benito Juárez, C.P. 03310
México D.F.
Mexico
Tel: (52) 55 91 83 1000
Fax: (52) 55 91 83 1000 Ext. 33945
diseno@senasica.sagarpa.gob.mx

Gilberto Granados Araiza
Oficina de Sanidad Agropecuaria
Aeropuerto International de Cancún
Cancún, Quintana Roo, C.P. 77500
Mexico
Tel: (52) 998 886 0136
oisacancun@prodigy.net.mx

UNITED STATES OF AMERICA

Edith Kennard
Staff Officer
United States Department of Agriculture
Food Safety and Inspection Service
Room 4865 South Building
1400 Independence Avenue, SW
Washington, DC 20250
United States
Tel: 202-720-5261
Fax: 202-720-3157
Edith.Kennard@fsis.usda.gov

F. Edward Scarbrough
U.S. Manager for Codex
United States Department of Agriculture
Food Safety and Inspection Service
Room 4861 South Building
1400 Independence Avenue, SW
Washington, DC 20250
United States
Tel: 202-205-7760
Fax: 202-720-3157
Ed.Scarbrough@fsis.usda.gov

Ellen Matten
Staff Officer
United States Department of Agriculture
Food Safety and Inspection Service
Room 4865 South Building
1400 Independence Avenue, SW
Washington, DC 20250
United States
Tel: 202-720-4063
Fax: 202-720-3157
Ellen.Matten@fsis.usda.gov

Megan Schildgen
International Program Specialist
United States Department of Agriculture
Foreign Agricultural Service
Room 3240 South Building, Mail Stop 1085
1400 Independence Avenue, SW
Washington, DC 20250
United States
Tel: 202-690-3985
Fax: 202-690-3982
Megan.Schildgen@fas.usda.gov

Jessica W. Maxwell
Program Assistant
United States Department of Agriculture
Foreign Agricultural Service
Room 3244 South Building, Mail Stop 1085
1400 Independence Avenue, SW
Washington, DC 20250
United States
Tel: 202-690-2993
Fax: 202-690-3982
Jessica.Maxwell@fas.usda.gov

Appendix II

DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 8 of the Elaboration Procedure)

Trichlorfon (Metrifonate) (insecticide)

Acceptable Daily Intake: 0-2 µg/kg bw (60th JECFA, 2003).

Residues: JECFA confirmed the MRL for cows's milk and the guidance levels for muscle, liver, kidney and fat of cattle recommended at the 54th meeting (WHO TRS 900, 2001).

Species	Tissue	MRL (µg/kg)	Step	JECFA	ALINORM
Cattle	Milk	50	8	54, 60	13 V, 14IV, 15 IV

Pirlimycin (antimicrobial agent)

Acceptable Daily Intake: 0-8 µg/kg bw (62nd JECFA, 2004).

Residues: Pirlimycin

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Cattle	Muscle	100	8	62	15 IV
Cattle	Liver	1000	8	62	15 IV
Cattle	Kidney	400	8	62	15 IV
Cattle	Fat	100	8	62	15 IV
Cattle	Milk	200 [(a)]	8	62	15 IV

[(a)] JECFA evaluated the effect of pirlimycin residues on starter cultures and for this reason recommended an MRL of 100 µg/kg of milk. Codex Members may therefore adapt national/regional MRLs in order to address this technological aspect for trade of fresh liquid milk intended for processing using starter culture.

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 recommended/considered.

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

Cypermethrin and alpha-cypermethrin (insecticide)

Acceptable Daily Intake: 0-20 µg/kg bw (62nd JECFA, 2004)

Residues: Total of cypermethrin residues (resulting from the use of cypermethrin or alpha-cypermethrin as veterinary drugs).

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Cattle	Muscle	50	8	62	15 IV
Cattle	Liver	50	8	62	15 IV
Cattle	Kidney	50	8	62	15 IV
Cattle	Fat	1000	8	62	15 IV
Cattle	Milk	100	8	62	15 IV
Sheep	Muscle	50	8	62	15 IV
Sheep	Liver	50	8	62	15 IV
Sheep	Kidney	50	8	62	15 IV
Sheep	Fat	1000	8	62	15 IV

Doramectin (anthelmintic)

Acceptable Daily Intake: 0-1 µg/kg bw (58th JECFA, 2002).

Residues: Doramectin.

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Cattle	Milk	15[(a)]	8	62	15 IV

[(a)] Depending on the route and/or time of administration the use of doramectin in dairy cows may result in extended withdrawal periods in milk. This may be addressed in national/regional regulatory programmes.

Appendix III

DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 7 of the Elaboration Procedure)

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

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

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	
Cattle	Liver	10	7	54, 58, 66	
Cattle	Kidney	2	7	66	
Cattle	Fat	18	7	54, 58, 66	13V, 14 IV

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 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

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 5 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	5	66	
Cattle	Liver	150	5	66	
Cattle	Kidney	200	5	66	
Cattle	Fat	150	5	66	
Cattle	Milk	50	5	66	
Sheep	Muscle	150	5	66	
Sheep	Liver	150	5	66	
Sheep	Kidney	200	5	66	
Sheep	Fat	150	5	66	
Sheep	Milk	50	5	66	
Goat	Muscle	150	5	66	
Goat	Liver	150	5	66	
Goat	Kidney	200	5	66	
Goat	Fat	150	5	66	
Pig	Muscle	150	5	66	
Pig	Liver	150	5	66	
Pig	Kidney	200	5	66	
Pig	Fat	150 [(a)]	5	66	
Chicken	Muscle	150	5	66	
Chicken	Liver	150	5	66	
Chicken	Kidney	200	5	66	
Chicken	Fat	150 [(a)]	5	66	
Chicken	Eggs	300	5	66	
Turkey	Muscle	150	5	66	
Turkey	Liver	150	5	66	
Turkey	Kidney	200 [(a)]	5	66	
Turkey	Fat	150	5	66	
Rabbits	Muscle	150	5	66	
Rabbits	Liver	150	5	66	
Rabbits	Kidney	200	5	66	
Rabbits	Fat	150	5	66	

[(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 recommended/considered.

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

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	5	62, 66	15 VI
Cattle	Liver	40	5	62, 66	15 VI
Cattle	Kidney	90	5	62, 66	15 VI
Cattle	Fat	10	5	62, 66	15 VI
Pig	Muscle	10	5	62, 66	15 VI
Pig	Liver	40	5	62, 66	15 VI
Pig	Kidney	90	5	62, 66	15 VI
Pig	Fat	10 [(a)]	5	62, 66	15 VI

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

Appendix V

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 4 of the Elaboration Procedure)

Flumequine (antimicrobial agent)

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

Residue Definition: Flumequine.

Species	Tissue	MRL (µg/kg)	Step	JECFA	ALINORM
Shrimps	Muscle	500 T [(a)]	4	66	

[(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 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

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 3 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	3	66	
Chicken	Liver	100	3	66	
Chicken	Kidney	100	3	66	
Chicken	Fat	100 [(a)]	3	66	
Chicken	Eggs	50	3	66	
Turkey	Muscle	100	3	66	
Turkey	Liver	100	3	66	
Turkey	Kidney	100	3	66	
Turkey	Fat	100 [(a)]	3	66	

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

Triclabendazole (anthelmintic)

Acceptable Daily Intake: 0-30 µg/kg body weight (40th JECFA, 1992).
Residue Definition: Keto-triclabendazole

Species	Tissue	MRLs(µg/kg)	Step	JECFA	ALINORM
Cattle	Muscle	150	3	40, 66	
Cattle	Liver	200	3	40, 66	
Cattle	Kidney	100	3	40, 66	
Cattle	Fat	100	3	40, 66	
Sheep	Muscle	150	3	40, 66	
Sheep	Liver	200	3	40, 66	
Sheep	Kidney	100	3	40, 66	
Sheep	Fat	100	3	40, 66	
Goat	Muscle	150	3	66	
Goat	Liver	200	3	66	
Goat	Kidney	100	3	66	
Goat	Fat	100	3	66	

Appendix VII

PROPOSED 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 5 of the Elaboration Procedure)

1. INTRODUCTION

1. Modern food production systems should be designed and managed to ensure that the exposure of food producing animals to veterinary drugs do 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 authorise, restrict or prohibit the use of veterinary drugs and to verify appropriate practices are being applied and sufficient controls are in place within the veterinary drug distribution and food production system as a whole to meet the appropriate level of health protection.

3. The application of a risk-based system to all food types should ensure the level of control and verification required is relative to the burden of risk that the food type contributes to consumers. The application of a risk-based approach across all food groups and hazard classes should allow a more focussed concentration of resources to those areas most likely to generate real health protection gains.

4. Risk profiles for different hazards may vary by country, region, species and/or production system. The application of a risk-based control and verification assurance system 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.

2. SCOPE

5. 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 associated with the exposure of animals to veterinary drugs in the production environment. 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 however should be read in conjunction with the principles outlined in this guide.

3. OBJECTIVES

6. To provide guidance on:

- The design and implementation of national control and verification programmes to assure that the residues associated with the use of and/or exposure to veterinary drugs are sufficiently controlled so that they are unlikely to have an adverse impact on the health of consumers of animal products.
- The elements and operation of import assurance programmes for residues of veterinary drugs.

4. DEFINITIONS

7. For the purposes of these guidelines:

Approved:	Officially authorised or recognised by a competent authority.
Production system:	Unit of production for which the assurance system has been designed. Will usually be a type of production within a country (or union of countries), but may be a smaller unit within a country able to be operated as a discrete unit.

Competent Authority(ies): For the most part this refers to the official government department(s) / agency(ies) responsible for the domestic food safety assurances associated with the use of veterinary drugs. However, this may involve other government agencies or other approved parties providing a specific market access assurance or an assurance for a specific segment of production.

Food harvest restriction / withholding period:

The recommended or mandated period or number of events which should occur subsequent to a defined exposure before food is harvested from the exposed animals or production system.

Risk-based Focussed on and proportionate to an estimate of the probability and severity of an adverse effect occurring in consumers.

PART 1: GENERAL CONSIDERATIONS

5. AIMS OF RESIDUE CONTROL AND VERIFICATION PROGRAMMES

i. To provide an assurance that food products of animal origin meet regulatory standards so that the health of consumers will not be adversely affected by residues of veterinary drugs.

ii. To facilitate trade.

6. GENERAL PRINCIPLES

8. Control and verification programmes for residues associated with veterinary drugs used or present on farms or feeds should:

i. Be risk-based.

ii. Be prevention focussed.

iii. Focus on realistic risk profiles assessed as reasonably likely to be associated with food derived from the relevant production system(s).

iv. Consider the possible risk profiles associated with approved, non-approved and prohibited veterinary drugs in the production system.

v. Be proportionate to the relative human health risk associated with these hazards compared with other food-associated hazards.

vi. Clearly identify the objectives of those standards or criteria which are not directly human health protection related.

vii. 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 make sure the inputs into and controls within their systems are appropriate to ensure that unsafe animal products will not be sold as a result of their action or inaction.

viii. Recognise that pre-harvest controls and practices will be primarily responsible for ensuring safe food.

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

x. Focus on system and population based assurances.

xi. Be cost effective and have the support of stakeholders.

7. PROGRAMME DESIGN CONSIDERATIONS

7.1 General Considerations

9. The production of animal products for human consumption is an integrated process with multiple parties contributing to the control of veterinary drug residues. The production of safe food relies on the various inputs and practices within the process being in control.

10. It is not only necessary to have knowledge of the types of veterinary drugs to which food producing animals are likely to be exposed in the production system but also what circumstances are necessary to result in a potential risk to consumers of foods derived from these production systems (the risk profiles).

11. Assurances with respect to the safety of a food production system include relevant practices and controls, and an effective verification programme in place to ensure food safety.

12. It is the day to day application of the practices and controls that is responsible for producing safe food rather than any animal or end product sampling and testing regime.

13. Monitoring tools are used to verify that the relevant controls are being implemented and are effective.

14. The relative importance of controls varies with the risk profile of individual hazards. Similarly the degree a system has to be out of control before public health may be compromised also varies between hazards. Accordingly, the scale and type of response to identified non-compliances will vary with the type of hazard and/or the risk profile involved.

7.2 Public Health Linkage

15. The primary objective of food safety authorities and this guideline is to ensure the use or exposure to veterinary drugs does not cause adverse health impacts in people consuming food products derived from those animals treated or exposed. Veterinary drugs are regulated in many countries for a variety of reasons. Some of the objectives are not directly related to the protection of the health of consumers of animal products, or the mandate of the Codex Alimentarius Commission.

16. Residues can exert an adverse effect on consumers in a number of ways. Most control systems have focussed on the potential for chronic toxicological adverse effects. Residues can also be associated with acute pharmacological effects on consumers or their Gastrointestinal Track (GIT) microflora, and/or allergic reactions. Different types of controls and monitoring systems may be justified where the registration risk assessment identifies one or more of these other end-points as being significant for human health associated with use of the veterinary drug in question. Detections of non-compliant residues justify regulatory action.

17. The Acceptable Daily Intake (ADI) is generally the amount of the compound and/or its metabolites that is estimated as able to be consumed on a daily basis for an entire lifetime by the most susceptible populations without adverse health affect. Where the level associated with the potential for an acute effect is less than that associated with a chronic toxicological effect then they will reflect this endpoint and will be further reduced by the appropriate safety multiples. Accordingly, the ADI concept is based on notional zero risk. Because of the high level of conservatism used in establishing ADIs, occasional ingestion of residues slightly exceeding the ADI generally should not pose a significant toxicological concern[1].

18. The maintenance of average consumption of residues over time under the ADI is an expression of the objective of a residue control and verification programme.

19. Maximum Residue Limits for Veterinary Drugs (MRLVDs)[2] are food/tissue specific. They are set at concentrations to ensure that consumers will not be exposed to residues that exceed the ADI even if they eat large quantities of the associated foods. They may be reduced further to be consistent with nationally established good practices in the use of veterinary drugs and or to reflect the extent to which practical analytical methods may be available.

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1 International Programme on Chemical Safety (IPCS) toxicological assessment monograph for food additives

2 As defined in the CAC Procedural manual

20. MRLVDs reflect the concentration of residue that should be achievable in the foods derived from treated animals if the veterinary drug is used as per the veterinary drug's label and foods are harvested from the animal production system after the recommended withdrawal period has expired. MRLVDs are the monitoring target for assessing the appropriateness and effectiveness of the practices and controls in place. Accordingly MRLVDs represent the maximum concentration recognised as acceptable in foods.

21. Different countries have different types and intensities of challenge of animal disease and accordingly, Good Practice in the Use of the Veterinary Drugs (GPVD) may also vary between countries. Lower tolerances than required to achieve the ADI may be set to reflect the use conditions associated with the local disease challenge profile within the production systems.

22. Individual importing countries may determine that higher tolerances than applied domestically may be acceptable for certain imports of foods of animal origin if the Competent authority can be conclude that such imports will not result in the ADI being exceeded[3].

7.3 Types of Verification Programme

23. Generally verification programmes can fall into three broad categories depending upon the criteria applied to the sample selection and/or their objectives; (a) system verification programmes, (b) risk-targeted verification programmes or (c) surveys.

(a) System Verification Programmes

24. The objective of system verification programmes is to provide information on the level of application of the practices and controls overall. As such they normally involve 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 level of control present in that population as a whole. They can focus on the level 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.

25. A combination of point of harvest testing coupled with direct audits of the various control points in the system can be used to reduce the amount of and reliance on chemical analysis while providing a higher level of assurance than point of harvest testing alone.

(b) Targeted Programmes

26. Targeted verification programmes involve the directed sampling of specific suppliers or products considered to pose a greater likelihood of not complying with one of the controls and/or having been found to have non-compliant residues detected.

27. Their objective is 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. Suppliers and/or product may be targeted due to for example:

- previous poor performance,
- breakdowns or absence of one of the quality system components usually relied on,
- other information,
- potential risk factors which may be correlated with an increased use of veterinary drugs such as high somatic cell counts in milk, or
- as a result of ante or post-mortem findings e.g. injection site lesions or resolving pathology.

28. While it is hard to derive general population based conclusions from targeted programmes, the operation of statistically based system verification programmes involving unbiased sampling in parallel with targeted verification programmes provides a greater level of assurance than the operation of either programme alone.

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[3] IPCS toxicological assessment monograph for food additives

(c) Surveys

29. Surveys are differentiated from system verification programmes mainly by their objectives and that they tend to be applied to sub-populations which may be linked by a common variable. Objectives of surveys may include the collection of base-line data for trend analysis or the collection of new data for consideration as to whether the development of additional controls and verification programmes may be appropriate. They are an appropriate tool to look more intensely at whether certain variables such as geographical position, season, or age may have an effect on the presence, absence or level of a residue.

(d) Other Verification Programmes

30. Domestic residue control and verification programmes may have other objectives not directly related to assuring food safety but these are outside the scope of this guideline.

PART 2: RECOMMENDATIONS

8. REVIEW AND RANKING OF HAZARDS

8.1 Introduction

31. Animals and/or production systems can be exposed to a variety of sources and types of chemicals that can potentially lead to residues in the products derived from them. However, not every one of these chemical inputs has the same potential to lead to a risk to the consumers of animal products derived from the production system. Hazard control is not the same as risk management.

32. In designing national control and verification programmes an understanding of the circumstances necessary for each chemical input to actually constitute a threat to consumers of animal products, along with a relative estimate of the likelihood of this occurring, are essential parts of the process of determining what controls and verification systems may be appropriate.

8.2 Types and Sources of Chemicals and Exposure Pathways

33. When reviewing and ranking the residues associated with the chemical inputs likely to be present at some stage in the production system it is firstly necessary to describe the potential sources and exposure pathways. For veterinary drugs, the type of residue and the pathways considered should not just be restricted to those sanctioned by the national regulatory authority but should also consider potential use of drugs in non-sanctioned ways or use of non-sanctioned drugs.

34. Types, sources and exposure pathways of chemicals may include:

Types and sources:

(a)	Veterinary drugs e.g.:	Approved / recognised drugs and uses
		Non-approved / non-recognised uses
		Illegal or non-recognised drugs

Exposure pathways:

(a)	Intended e.g.:	Direct administration to the animals
		Indirect administration to the animals through addition to feed or water.
(b)	Unintended e.g.:	Feed or water contamination
		Environmental contamination

8.3 Risk Profile Considerations

35. After the potential types, sources and exposure pathways of chemical inputs into the production system have been identified, it is then necessary to consider what are the circumstances required for each of these to cause an adverse health impact on consumers, as well as the likelihood of such circumstances occurring in the absence of a control.

36. Such considerations will include:

- What type of hazard is associated with the chemical input e.g. chemical residue, biological residue or pathology, greater chance of resistant bacteria or physical remnant.
- The class and severity of the adverse health effect associated with it e.g. chronic toxicity, acute pharmacological, allergic reaction, or microbiological disturbance.
- What use and/or production circumstances are necessary, and what is the likelihood of these occurring, for the residue to be in foods derived from the production system at concentrations and frequencies approaching those which could pose an actual risk to human health.
- What consumption circumstances are necessary for the residue to actually constitute a risk to consumers of animal products.

9. CONTROL POINTS

9.1 Introduction

37. Most controls available tend to attempt to mediate what and how animals or production systems are exposed to chemicals, or the time between a known exposure and subsequent harvest of animal products.

38. Restrictions and recommendations however are only part of the control system. These are only as good as the knowledge, practices, skills and motivation of those administering the compounds, or those of the feed compounders, and how effectively any harvest restriction stays identified with the exposed animals or product and is communicated to subsequent purchasers.

9.2 Regulatory Framework for Use of Veterinary Drugs

39. The regulatory framework for sale and use of veterinary drugs should be specified in law. Restrictions on what formulations can be used and how they can be used is a key control point. Similarly, imposition of time or event based harvest food restrictions subsequent to the last exposure can also be used to mitigate potential risks.

40. For veterinary drugs it is important that the competent authority tasked with providing consumer assurances for foods has a sufficient level of control over and knowledge of what veterinary drugs are being sold and used within the production systems.

41. All formulations of veterinary drugs manufactured or imported into the country should be required to be recorded on a national register before being able to be used.

42. Appropriate approval criteria should be established for such formulations to be added to this list. These approval criteria may accept the assessments of other recognised competent authorities where use patterns are likely to be similar.

43. Those formulations not on these lists should not be allowed to be used and sufficient sanctions need to be in place to act as a deterrent. National regulations should be established to enforce what veterinary drugs may be sold domestically and how these may be used.

44. It is important that the approval and registration systems are both efficient and as far as possible meet the needs of the producers so as to reduce the motivation for alternative product sourcing networks to develop.

45. Information and/or education programmes regarding the suitable use for both efficacy and the protection of consumers need to be supplied and/or provided for each formulation.

46. For certain drugs it may also be appropriate, where justified by an appropriate risk characterisation, to have further sale and use conditions mandated to help ensure appropriate use and to prevent misuses or abuses. Such additional controls should be targeted at managing specifically identified risks and should be regularly checked as appropriate to the risk posed for both their efficacy and necessity. They may include for example:

- Requiring all sales to be subject to a prescription from a regulatory or professional body/person,
- Restricting administration to individuals or professions with prescribed competencies,
- Requiring all treated animals / production systems to be identified in specified ways,
- Requiring all uses to be recorded and/or notified to (a) central database(s).

47. Both the continued efficacy and the necessity of any such additional controls should be reviewed against the local risk profile to ensure they don't act in a counterproductive fashion by motivating alternative product sourcing and use to develop.

48. In a risk-based system it is also desirable that the competent authority(ies) be able to derive estimates of both the level and most common types of uses of each veterinary drug.

9.3 On-farm Recommendations

(a) Use of Veterinary drugs

49. Producers should only use veterinary drugs which have been approved for use in food producing animals. Non-approved veterinary drugs should not be used (except as provided for in the next paragraph). Veterinary drugs should be used strictly in accordance with the officially approved / recognised instructions.

50. Veterinary drugs should only be used off-label 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.

51. Excepting situations covered by the above paragraph, only those veterinary drugs specifically approved for use in lactating animals, layer hens and honeybees should be used in animals when milk, eggs or honey, respectively, are collected for human consumption.

(b) Assurance Systems

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

53. All treated or exposed animals, or lots of animals, need to be positively identified as being subject to food harvest restrictions for the period for which they apply (slaughter/harvest/milk withholding period).

54. Records should be kept of all details of the treatment and the length of time and/or number of milkings required before the animal or product from the animal can be harvested for human consumption.

(c) Additional advice regarding lactating animals:

55. The food safety assurance measures need to be structured to be responsive enough to be able to provide sustainable assurances on a daily basis that milk is harvested only from those animals considered to have an acceptable residue status.

56. Discarded milk should not be fed to other animals unless appropriate controls are in place to assure food for human consumption from these animals will not be harvested before any transferred residues have fallen to acceptable concentrations.

57. Ideally, treated or exposed animals in large herds should be kept separate from those animals not under restrictions to help reduce the potential for mistakes. Animals under harvest restrictions should ideally be milked after the rest of the herd.

58. Animals under milk harvest restrictions should be milked in such a way that ensures their milk does not mix with milk being harvested for human consumption. Any equipment used needs to be able to be adequately cleaned prior to being used on other animals.

9.4 Communications with subsequent purchasers

59. It is important that any food harvesting restrictions still in place on the animal or animal product at the time of sale be communicated to subsequent purchasers of the animal(s) or products derived from them.

60. Processors should be held accountable for ensuring that they only purchase and/or process animals and/or animal products from suppliers who can credibly attest to the suitability/safety of the animal or animal product for the purpose intended.

61. Where animals or animal products are supplied to processors by other than the primary producer then these suppliers should be held accountable by processors to show that they have due knowledge that the animal or animal product is no longer under any relevant restriction.

10. VERIFICATION

10.1 Principles and the Role of Verification Programmes

62. The overall objective of the implementation of verification programmes is: To provide an appropriate level of confidence that the practices and controls in place are appropriate and being applied to the extent necessary to ensure that the health of consumers of animal products will not be adversely affected by any veterinary drug residue inputs into production systems.

63. Systems should focus on pre-harvest practices and controls, not post-harvest testing

64. The frequency and intensity of verification / audit should depend on the performance of the sector and the level of non-compliance that may lead to a significant human health risk.

65. Verification programmes may be designed to assess the effectiveness of a control system or to target compliance by individuals or groups.

66. A combination of direct audits of the various control points in the system coupled with point of harvest testing will provide a higher level of assurance than point of harvest testing alone. Such combinations can be used to reduce both the amount of and reliance on chemical analyses.

67. Similarly, the operation of statistically based system verification programmes involving non-biased sampling in parallel with verification programmes targeted at specific suppliers or product will provide a greater level of assurance than the operation of either programme alone.

68. While the sample sizes for system verification programmes can be statistically pre-determined (see Part One for additional guidance), the number of risk-targeted samples will vary according to the frequency at which the profiling attributes present themselves.

10.2 Examples of design considerations for verification programmes

69. As appropriate to the pre-determined risk profiles in the country and/or production system, verification programmes may be used to help evaluate the:

- validity of the assumptions used during the registration process;
- existence or non-existence of alternative unacceptable production, marketing and/or advice chains;
- effectiveness of veterinary drug label information (Good Practice in the use of Veterinary Drugs – (GPVD)) as a human health risk mitigation tool, and how well the use recommendations correlate with actual uses of, or needs for, the product;
- effectiveness of other education or risk mitigation programmes;
- efficacy of any feed medicating quality systems;

- effectiveness of animal production and animal sales quality systems as they relate to animal identity and information transfer on any food harvest restrictions;
- application and effectiveness of corrective actions;
- significance of environmental and/or natural contaminants.

10.3 Audit of Pre-Harvest Control Points

70. Pre-harvest and/or pre-processing quality assurance and verification programmes may be used to reduce the reliance on post-harvest verification programmes such as chemical analysis.

71. On-farm sampling may also be used where the risk profile assessment has identified that there are specific concerns associated with the use of substances prohibited by the competent authority.

72. As appropriate to the pre-determined risk profiles in the country and/or production system, the following potential pre-harvest control points may be considered for a level of audit in the verification programme.

- The sellers and purchasers of veterinary drugs to verify what is being sold and how they are being marketed.
- 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.
- The animal and animal product sale systems to verify whether and how any food harvest restrictions associated with the animal or product is being communicated.
- 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.

10.4 Point of Harvest Verification Programmes

(a) General Considerations

73. Post-harvest verification programmes of the actual levels and frequency distributions of residues present in animals or products at the point of harvest should be established in addition to one or more of the aforementioned pre-harvest verification programmes. Both system and risk-targeted verification programmes should be used in parallel.

74. The frequency and intensity of verification / audit of each drug residue chosen to be monitored under the system verification programme should depend on its risk profile, the previous performance of the sector and the nature of non-compliance.

75. Where non-biased samples are selected from the general population it should not be necessary to retain lots of production associated with randomly selected samples pending the availability of the analytical results as the results are representative of a wider proportion of the general population.

76. For targeted verification programmes, where it is considered that both the likelihood and human health significance of a potential non-compliance poses an unacceptable risk then all associated product should be retained until sufficient information can be generated to provide the required level of assurance.

(b) Sample Taking

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

78. Samples should ideally be taken before animals and/or products are commingled with animals or product from other suppliers. For lactating animals samples should ideally be taken at the time the milk is collected from the farm.

79. Each sample needs to be clearly identified with the unit of production and the supplier that it represents so that appropriate trace-back and follow-on actions can be applied should a non-compliant result be found.

80. The identity and integrity of what the sample is meant to represent also needs to be maintained throughout the sampling, storing, shipping, analysis and reporting process.

(c) Laboratories

81. The laboratories used should have in place a suitable quality assurance programme and they should have validated all methodologies used to an appropriate level relative to their role within the monitoring programme.

82. The performance characteristics of each of the methods used by the laboratories should be pre-agreed with the competent authority requiring the testing and should be set to reflect the objectives of the specific part of the programme. Regulatory reporting thresholds for laboratories should be pre-agreed with the competent authority and should only be set as low as that specifically determined by the competent authority as being required to meet its public health objectives.

10.5 Analytical Results

(a) Reporting of results

83. Laboratory results should be interpreted in conjunction with the performance characteristics of the method including measurement uncertainty of analytical results. Laboratories should be required to provide this information when reporting potentially non-compliant results.

84. Laboratories should also report all incidences where unusual extraneous substances were detected but for which the identity was unable to be confirmed.

(b) Analysis of results

85. Each non-compliant result should be analysed to ascertain what contributing factors lead to its occurrence and the systemic significance of the identified case.

86. All detections of unidentified substances should also be considered for possible further follow-up.

87. Depending on the results of this analysis, a consideration of whether and what local and/or systemic corrective actions are appropriate to prevent reoccurrence.

88. When an animal tissue has a residue in excess of the relevant MRL at the point of harvest it can mean one of a number of things, not all of which are in the direct control of the producer or supplier. These include:

- The veterinary drug was not used according to label or prescription instructions.
- A non-authorised veterinary drug or formulation was used.
- The minimum post-treatment food harvest restriction / withdrawal period was not observed (failure to maintain the identity of restricted animals or animal products is often a factor here).
- An unintended feed, water or environmental exposure occurred.
- The food / feed harvest withholding period recommendation on the label is not fully appropriate.
- The food / feed came from one of the small percentage of animals that statistically are predicted will have residues in excess of the MRL even after the food harvest restriction / withdrawal period has elapsed.
- Analytical method problems.

89. Some results may reflect an issue more appropriately addressed by the veterinary drug / pesticide registration or recognition system.

10.6 Regulatory responses to identified non-compliances

90. Where the analysis indicates a significant local or systemic control failure, this should elicit an appropriate corrective reaction from the entire segment of the population potentially similarly affected or motivated. Sufficient restrictions and targeted verification should then be put in place so as to be able to assure appropriate corrective actions have been put in place and are being applied. The time scale for taking such actions and the intensity of any reaction will vary according to the health significance of any unacceptable level and frequency of non-compliances found. Non-compliant product should not be passed for human consumption.

91. In many cases a determination as to whether the incident(s) are the result of isolated mistakes or whether they represent an unacceptable level of negligence or wilful non-observance of the recommended / mandated conditions of use will influence the regulatory or commercial reaction. Similarly the identification of the failure of a control point outside the direct control of the producer or supplier (such as registration issues) may also necessitate a different reaction if long-term solutions are to be found.

92. For isolated mistakes the provision of appropriate advice and motivation for the relevant sector to make the necessary improvements to the controls and practices may be an appropriate response. This should of course be coupled with a level of follow-up verification that appropriate corrective actions have been put in place and are being applied e.g. through heightened analytical surveillance activity.

93. Where an unacceptable level of negligence or wilful non-observance of the recommended / mandated conditions of use is determined as being the cause, publicly promoted punitive reactions (e.g. condemnations, fines, movement controls etc) may also be appropriate and have some wider deterrent value. This is in addition to the provision of appropriate advice and/or motivation for the sector to make the necessary changes along with an appropriate level of subsequent verification that sufficient corrective actions have been put in place and are being applied.

94. Where the analysis identified a significant contribution due to a control point failure outside the producer's / supplier's direct control (e.g. registration / label issues) then appropriate actions should be taken to ensure the sector responsible for the control takes the necessary corrective actions to prevent an unacceptable level and/or frequency of recurrence.

95. For farm targeted verification programmes: Where the results from the sampled portion of the lot does not provide the necessary confidence that the rest of the lot has been produced with a sufficient application of appropriate practices and controls, the lot should not be passed for human consumption until sufficient information can be generated to provide the required level of assurance as to its safety.

96. For non-biased sampling programmes: The results of non-biased sampling of the general population are a measure of the effectiveness and appropriateness of the controls and practices within a wider segment of the production system. Accordingly they should be used for an assessment as to whether one of the controls within the system may need adjusting, and should not be routinely used or relied upon for product disposition judgements. Where the results indicate there is a direct risk to public health, an attempt should be made to trace and remove all similarly affected product. In making such judgements it needs to be acknowledged that the non-compliant result represents only a small proportion of the total production likely to be similarly affected and not as yet identified. The unidentified proportion likely represents a much greater potential threat to consumers than the identified "lot". 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.

97. Where pre-harvest controls cannot be relied upon due to their non-existence or an unacceptably high level of non-compliance by animal food producers, a higher level of post harvest verification may be appropriate in order to attempt to be able to provide the required level of consumer assurance. This should be regarded as an interim measure only until the appropriate corrective actions to the control system have been put in place and subsequently demonstrated to be effective.

98. 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. Where a significant level of non-compliance is identified in any one year and consequent changes to the control programme implemented, a higher level of verification should be considered for the subsequent year to help assure the appropriateness of the changes to the resolution of the problem. Some of the selected lower risk profile compounds should be considered for rotation in and out of the programme based on performance to ensure as wide as possible scope is covered.

PART THREE

11. INTERNATIONAL ASSURANCES

99. As with national programmes, it is the practices and controls in place in the exporting country rather than port of entry testing that best ensures safe food. Communication and co-operation between the relevant competent authorities can be used to deliver higher-level assurances than sole reliance on port of entry inspection programmes. To help facilitate trade from developing nations, the potential for longer phase-in times and increased cooperation, and possible technical assistance across all aspects of programme development and operation, should be considered.

(a) Exchange and review of control and verification programmes

100. The application of a risk-based control and verification assurance system should provide the necessary basis for exporting countries to certify, where required, the safety of exported food, and for importing countries, subject to any assessment they deem necessary, to have the confidence to accept such consignments.

101. Trading countries should be encouraged to exchange copies of their control and verification programmes along with the results of the preceding years on a regular basis. In any review, it needs to be noted that risk profiles and management options may vary substantially between countries. The appropriateness of the control and verification assurance system to the risk profiles and circumstances existing in the exporting country relevant to the level of human health protection required by the importing country is the relevant consideration, not how closely it may or may not mirror the control and verification system in the importing country.

102. Where either the risk profile of the exporting country, and/or the level of health protection of the importing country, is significantly higher (e.g. where one country has a substantially lower ADI) additional controls and verification may be required.

103. The same risk-based principles should apply to export assurance programmes as have been applied to the design and implementation of national assurance programmes. Where deemed appropriate, targeted quality assurance programs may be used to deliver the higher level of assurance required for the specific segment of production.

(b) Port of entry testing programmes

104. The assurances able to be gained from countries providing copies of their control and verification programmes and the subsequent certification that product has been produced in accordance with the programmes is much greater than able to be gained from port of entry inspection programmes. In such cases the role of port of entry testing programmes, should they be considered necessary, changes from being a primary measure of product acceptability to that of being a secondary system verification tool.

105. It is worthy to note that the tissue / fluid matrices used for national verification programmes may vary from those used in port of entry programmes e.g. milk versus processed dairy products. The process, processing aids and/or other additives may on occasion introduce confounding variables. It is important that any analytical methods used are fully validated for the specific matrix analysed.

106. 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 performance. Consignments of animal products tend to be heterogeneous by nature and will often be made up of commingled product from a variety of animals, farms and processing dates. Results will reflect the performance of the production system as a whole and should not be extrapolated to specific judgements on other units within the consignment except where a common pre-harvest risk factor is shared and a direct health threat is indicated.

107. Samples need to be clearly identified with both the consignment and the sub-unit of the consignment actually sampled to allow exporting countries to be able to fully trace their origin back should a non-compliant result be found. The recording of commercial information such as bar codes can often help this process. The identity, integrity and security of the sample need to be maintained throughout the sampling, storing, shipping, analysis and reporting process. Unprocessed proportions of the sample need to be maintained sufficient to allow possible independent confirmation of the finding should a dispute result. When non-compliant results are reported appropriate information as to the confidence interval of the result, a description of the method used and the performance characteristics of the method of analysis should be provided to all parties affected by the result (e.g. the owner of the consignment and the certifying competent authority).

108. If both parties testing programmes are working effectively then the results of port of entry testing programmes should broadly correlate with the findings of the exporting country's own verification programmes. All results should be reported back to the competent or certifying authority of the exporting country. The competent authority from the exporting country should conduct a traceback and apply appropriate corrective actions and provide a summary of these to the importing country.

109. Where the type, level and/or frequency of non-compliance detected raises concerns as to whether the imports are meeting the level of human health protection required by the importing country, then additional assurances may be requested. The importing country may also choose to increase the level of port of entry verification to confirm that the assurances given are in fact addressing the problem. Targeted sample and hold programmes should be reserved for those situations where it is assessed that a direct risk to human health exists associated with directly related lots of food of animal origin that has not been able to be subjected to further control by the competent authority of the exporting country.

110. Where residues of prohibited substances are found, the competent authorities of both the importing and exporting country should cooperate to work towards isolating any potentially similarly affected food of animal origin and resolving any wider control problem should it be found to exist. Resolution of such problems will require an analysis in the originating country of exactly where, how and why such residues are finding their way into the production system, what may have gone wrong within the country's own control and monitoring system, and subsequent application of appropriate additional controls to address the situation. 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.

111. The application of new sampling and testing methodologies can also on occasion reveal types and levels of residues previously unknown to exist by one or both parties. The determination of where, how and why such residues are finding their way into the production system and their significance again may take some time. Where the presence of such residues is associated with previously accepted production practices, the implementation of changes, should these be deemed necessary, may need to be implemented over an extended period of time. Especially 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.

112. In all cases the competent authorities should co-operate to ensure the health of consumers of both countries is protected.

PART FOUR

12. SAMPLING PROTOCOL DESIGN AND PLANNING: STATISTICAL CONSIDERATIONS

12.1 INTRODUCTION

113. The Codex Alimentarius Commission has decided that recommended sampling procedures for food additives, pesticide residues and 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 - Normal Practice. Accordingly the following guidelines have been written. It is important to note that this section does not just apply to the sampling associated with laboratory analyses but is also broadly relevant to all verification and auditing programmes contributing to the assurance programme.

12.2 PRINCIPLES

- The purpose of the verification programme needs to be clearly defined.
- The population being sampled and to which the results apply needs to be defined.
- Whether the sampling is non-biased or targeted (directed), and the criteria to be applied to the analysis of the results need to pre-determined.
- Sample sizes for non-biased sampling protocols should be statistically based
- The targeting criteria applied to direct sampling need to be pre-determined.
- Each sample needs to be clearly identified with the unit of production and the supplier it represents
- The identity, security and integrity of the sample need to be maintained throughout the sampling, storing, shipping, analysis and reporting process.
- Unprocessed proportions of the sample need to be maintained to allow possible independent confirmation of the finding should a dispute result.

11.3 GENERAL DESIGN CONSIDERATIONS

114. 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. Generally sampling protocols have a low efficacy to be able to detect low levels of non-compliance so where such levels are considered potentially a significant risk to human health other assurance programmes are far more important.

12.4 POPULATIONS OF INTEREST

115. 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 level 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 e.g.

- the seller of the chemical input into the production system,
- the producer,
- the supplier of the animals or animal product to the processor, or
- the processor .

116. 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.

117. 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, then several production seasons or calendar years may be used / needed to collect the number of samples statistically determined to give the required level of confidence.

118. 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.

12.5 POINT OF SAMPLING

119. 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 level, 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.

120. On-farm sampling may also be used as part of an ante-mortem quality assurance programme or where there are concerns associated with the possible use of substances prohibited by the competent authority.

121. 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.

122. 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 level of non-compliance. The below referenced statistical tables are not relevant to such programmes and sample sizes should reflect the importing country's confidence in the performance of the exporting country.

123. For port of entry testing programs the population of interest is all like product produced under a common control and verification system. 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 system 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 system.

12.6 NON-BIASED VERSUS TARGETED SAMPLING: SAMPLE SIZE CONSIDERATIONS FOR PRIMARY VERIFICATION PROGRAMMES

124. Non-biased sampling is designed to provide profile information, especially as to the level of application or performance of a control or control system for a specified animal / food population over a defined period (usually annual).

125. 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 level of confidence to be placed in the results as well as economic considerations.

126. If the size of the population is small then the effect of sampling without replacement should not be ignored and the sampling distribution should be based on the hypergeometric distribution. However most populations sampled using non-biased sampling will tend to have larger than 5000 units and the effect of sampling without replacement (hypergeometric) and sampling with replacement (binomial) becomes small and the binomial distribution can be used to determine an appropriate sample size. Regardless of the size of the population sampled, the required sample size based on the binomial distribution will always be equal to or greater than the required sample size based on the hypergeometric distribution.

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

128. Where non-compliant results are detected it is possible to derive a crude estimate of the likely prevalence in the general population. However, where no non-compliant results are found then any statements about prevalence need to be stated as a confidence level that the prevalence of non-compliant results does not exceed a specified percentage. The sample size required to give a required level of 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 (e.g. 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

129. 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 and can exert a significant adverse health effect on the consuming public at these levels.

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

Prevalence (%)	**Number of animals 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								

130. 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. As it is just a sub-population which is considered to have greater chance of non-compliance is being sampled it is not possible to extrapolate any non-compliant results to make conclusions about the general population. However, where compliant results are found these results in conjunction with non-biased program results provide a higher level of assurance that the residue control system is working at an appropriate level of control.

131. The application of directed or targeted sampling in port of entry sampling programmes is only appropriate where product is known to or suspected of sharing the same exposure profile. As animals are exposed to veterinary drugs prior to any product being harvested, any directed sampling at port of entry should be reserved for situations where sub-populations of product likely to have shared a similar pre-harvest exposure profile can be identified. However, following the detection of non-compliant results during port of entry programme, 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.

Appendix A

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN ANIMALS, ANIMAL PRODUCTS AND ANIMAL-DERIVED FOODS (EXCEPT HONEY)

1. OBJECTIVE

133. To provide instructions for sampling a lot of animals (including fish), animal products or animal-derived foods to determine compliance with Codex Maximum Residue Limits for Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 LOT

134. [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.]

2.2 CONSIGNMENT

135. [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.]

2.3 PRIMARY SAMPLE

136. 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).

2.4 BULK SAMPLE

137. The combined total of all the Primary Samples taken from the same Lot.

2.5 FINAL (LABORATORY) SAMPLE

138. The Primary or Bulk sample, or a representative portion of the Primary or Bulk Sample, intended for laboratory analysis.

2.6 LABORATORY TEST PORTION

139. 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.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 Selected Class B: Primary Food Commodities of Animal Origin

Type 06 Mammalian Products

No. 030 Mammalian Meat

No. 031 Mammalian Fats

No. 032 Mammalian Edible Offal

No. 033 Milks

Type 07 Poultry Products

No. 036 Poultry Meats

No. 037 Poultry Fats

No. 038 Poultry Edible Offal

No. 039 Eggs

Type 08 Aquatic Animal Products

No. 040 Freshwater Fish

No. 041 Diadromous Fish

No. 043 Fish Roe and Edible Offal of Fish

No. 045 Crustaceans

Type 09 Amphibians and Reptiles

No. 048 Frogs, Lizards, Snakes and Turtles

Type 10 Invertebrate Animals

No. 049 Molluscs and Other Invertebrate Animals

3.2 Selected Class E: Processed Products of Animal Origin made from only Primary Food Nos. 030, 032, 036, and 038

Type 16 - Secondary Products

Type 17 - Derived Edible Products of Aquatic Animal Origin

Type 18 - Manufactured (single ingredient) Products of a Minimum of One Kilogram Container or Unit Size

Type 19 - Manufactured (multiple ingredient) Products of a Minimum of One Kilogram Container or Unit Size

4. PRINCIPLE ADOPTED

140. For purposes of control, the MRLVD is applied to the residue concentration found in each Laboratory Sample taken from a Lot. Lot compliance with a Codex 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.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

141. Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 PRODUCT TO SAMPLE

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

6.2 PRECAUTIONS TO TAKE

143. During collection and processing, 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, must be prevented.

6.3 COLLECTION OF A PRIMARY SAMPLE

144. Detailed instructions for collection of a Primary Sample of various products are provided in Tables A and B. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Table A: Meat and Poultry Products; 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 multiple animals are required for adequate sample size of the Primary Sample (i.e., poultry organs), the samples should be collected consecutively after random selection of the starting point.

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.

- Unopened cans or packages which constitute a Final (Laboratory) Sample should be sent unopened and intact to the laboratory for analysis.

e. The contents of cans or packages opened by the authorised inspector should then be frozen as described in paragraph 6.8.d before dispatch to the laboratory for analysis.

f. Large, bone-containing units of product (i.e., prime cuts) should be sampled by collecting edible product only as the Primary Sample.

g. Remaining portions of Final (Laboratory) Samples, after removal of Laboratory Test Portions for analysis, should be frozen and stored in conditions which will maintain the sample integrity.

6.4 THE NUMBER OF PRIMARY SAMPLES TO COLLECT FROM A LOT

145. The number of Primary Samples collected will vary depending on the status of the Lot. A Lot may be considered suspect if there is a history of non-compliance with the MRLVD, evidence of contamination during transport, signs of toxicosis observed during ante- or post-mortem inspection, or other relevant information available to the authorised inspection official. If there is no reason to suspect adulteration, the Lot is designated as non-suspect.

6.4.1 Sampling Suspect Lots

146. A minimum of six to a maximum of thirty Primary Samples should be collected from a Suspect Lot. When the suspected adulteration is expected to occur throughout the Lot or is readily identifiable within the Lot, the smaller number of samples is sufficient.

6.4.2 Sampling Non-Suspect Lots

147. A statistically-based, non-biased sampling programme is recommended for Non-Suspect Lots. Any of the following types of sampling can be used.

a. Stratified Random Sampling

148. In a complex system where commodities must be sampled at many locations over extended time periods, it is very difficult to apply simple random criteria in the design of a sampling programme. A useful alternative sampling design is Stratified Random Sampling which separates population elements into non-overlapping groups, called strata. Primary Samples are selected within each stratum by a simple random design. 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. Time strata (e.g., month, quarter) are commonly used for convenience, efficiency, and detection of seasonal variability. Random number tables 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.

b. Systematic Sampling

149. Systematic Sampling is a method of selecting a sample from every 'K' quantity of product to be sampled, and then sampling every 'K' unit thereafter. Systematic Sampling is quicker, easier, and less costly than non-biased sampling, when there is reliable information on product volumes to determine the sampling interval that will provide the desired number of samples over time. If the sampling system is so predictable that it may be abused, it is advisable to build some randomness around the sampling point within the sampling interval.

c. Biased or Estimated Worst Case Sampling

150. In Biased or Estimated Worst Case Sampling, the investigators should use their judgement and experience regarding the population, Lot, or sampling frame to decide which Primary Samples to select. As these are non-random samples, no inferences should be made about the population sampled from the data collected. The population group anticipated to be at greatest risk may be identified. Exporting countries should conduct a comprehensive residue control programme and provide results to importing countries. Based on an importing country's data, testing may be conducted as applied to non-suspect products. Countries that do not provide residue testing results showing compliance with MRLVDs should be sampled as suspect lots.

6.5 PREPARATION OF THE BULK SAMPLE

151. The Bulk Sample is prepared by combining and thoroughly mixing the Primary Samples.

6.6 PREPARATION OF THE FINAL (LABORATORY) SAMPLE

152. The Primary or Bulk Sample, or a representative portion of the Primary or Bulk Sample, which constitutes the Laboratory Sample, should be submitted to the laboratory for analysis.

153. Some national legislation 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 in Section 6.2 should be observed.

6.7 PREPARATION OF THE LABORATORY TEST PORTION

154. The Laboratory Test Portion should be prepared from the Final (Laboratory) Sample by an appropriate method of reduction.

6.8 PACKAGING AND TRANSMISSION OF FINAL (LABORATORY) SAMPLES

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.

d. For shipping, all perishable samples should be frozen to minus 20^{o}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^{o}C prior to dispatch.

e. Replicate portions of the Final (Laboratory) Sample which may be retained as required by national 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.

7. RECORDS

155. 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.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

156. If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

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
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

TABLE A: MEAT AND POULTRY PRODUCTS		
Commodity	**Instructions for collection**	**Minimum quantity required for laboratory sample**
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
D. Fresh/chilled or frozen parts		
1. Wholesale packaged a. Large parts b. Small parts	 Collect an interior unit from a selected container. 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

TABLE A: MEAT AND POULTRY PRODUCTS		
Commodity	**Instructions for collection**	**Minimum quantity required for laboratory sample**
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.
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 analyzed 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, pasteurized, 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 Semiskimmed	As for whole liquid milk.	500 mL
B. Evaporated milk evaporated full cream & skimmed milk	Bulk containers (barrels, drums). Mix the contents carefully and scrape adhering material from the sides and bottom of the containe Remove 2 to 3 litres, repeat the stirring and take a 500 mL sample. 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

TABLE B: MILK, EGGS, DAIRY PRODUCTS AND AQUATIC ANIMAL PRODUCTS		
Commodity	**Instructions for collection**	**Minimum quantity required for laboratory sample**
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
C. Butter oil including anhydrous butte roil and an-hydrous milkfat	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

TABLE B: MILK, EGGS, DAIRY PRODUCTS AND AQUATIC ANIMAL PRODUCTS		
Commodity	**Instructions for collection**	**Minimum quantity required for laboratory sample**
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
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 shellfish	Collect 12 sub samples randomly.	1000 g
D. 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

Appendix B

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN HONEY

1. OBJECTIVE

157. To provide instructions for sampling a lot of honey to determine compliance with Codex Maximum Residue Limits for Residues of Veterinary Drugs (MRLVDs).

2. DEFINITIONS

2.1 LOT

158. [An identifiable quantity of food (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. Several Lots may make up a consignment.]

2.2 CONSIGNMENT

159. [A quantity of food (honey) as described on a particular contractor's shipping document. Lots in a Consignment may have different origins or may be delivered at different times.]

2.3 PRIMARY SAMPLE

160. 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.

2.4 BULK SAMPLE

161. The combined total of all the Primary Samples taken from the same lot.

2.5 FINAL (LABORATORY) SAMPLE

162. The Primary or Bulk sample, or a representative portion of the Primary or Bulk sample, intended for laboratory analysis.

2.6 LABORATORY TEST PORTION

163. 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.

3. COMMODITIES TO WHICH THE GUIDELINE APPLIES

3.1 SELECTED ACCORDING TO ORIGIN

164. Blossom or nectar honey that comes mainly from nectaries of flowers.

165. Honeydew honey that comes mainly from secretions of or on living parts of plants.

3.2 SELECTED ACCORDING TO MODE OF PROCESSING

166. Comb honey that is stored by bees in the cells of freshly built broodless combs, and sold in sealed whole combs or sections of such combs.

167. Extracted honey that is obtained by centrifuging decapped broodless combs.

168. Pressed honey that is obtained by pressing broodless combs with or without the application of moderate heat.

4. PRINCIPLE ADOPTED

169. For purposes of control, the maximum residue limit (MRLVD) is applied to the residue concentration found in each Final (Laboratory) Sample taken from a Lot. Lot compliance with a Codex MRLVD is achieved when none of the Final (Laboratory) Samples contain a residue greater than the MRLVD.

5. EMPLOYMENT OF AUTHORIZED SAMPLING OFFICIALS

170. Samples must be collected by officials authorized for this purpose.

6. SAMPLING PROCEDURES

6.1 PRODUCT TO SAMPLE

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

6.2 PRECAUTIONS TO TAKE

172. During collection and processing, contamination or other changes in the samples must be prevented which would alter the residue, affect the analytical determination, or make the Final (Laboratory) Sample not representative of the Bulk Sample.

6.3 COLLECTION OF A PRIMARY SAMPLE

173. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements and detailed instructions for collection of a primary sample of honey are provided in Appendix B, paragraph 9. The following are general instructions.

a. Each Primary Sample should be taken from a single unit in a Lot, and when possible, be selected randomly.

b. 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 Primary Sample should contain a representative portion of the product. Each sample should be prepared for analysis as referenced in paragraph 6.5.

6.4 THE NUMBER OF PRIMARY SAMPLES TO COLLECT FROM A LOT

174. The number of Primary Samples collected will vary depending on the status of the Lot. If adulteration is suspected by origin from a source with a past history of residue non-compliances with the MRLVD, by evidence of contamination during transport or by the availability of other relevant information to the authorised inspection official, the Lot is designated a suspect Lot. If there is no reason to suspect adulteration, the Lot is designated a non-suspect Lot.

6.5 PREPARATION OF THE PRIMARY SAMPLE

175. The Primary Sample is prepared as described in Part Four.

6.6 PREPARATION OF THE FINAL (LABORATORY) SAMPLE

176. The Primary Sample (or the Primary Samples pooled as a Bulk Sample) should, if possible, constitute the Final (Laboratory) Sample. The Final (Laboratory) Sample should be submitted to the laboratory for analysis. If the Primary Sample (or Bulk Sample from pooled primary Samples) is too large to be submitted to the laboratory, a representative sub sample should be prepared. Some national legislation may require that the final sample be sub-divided into two or more portions for separate analysis. Each portion should be representative of the Final (Laboratory) Sample. Precautions in Section 6.2 should be observed.

6.7 PREPARATION OF THE LABORATORY TEST PORTION

177. The Laboratory Test Portion should be prepared from the Final (laboratory) Sample by an appropriate method of reduction.

6.8 PACKAGING AND TRANSMISSION OF FINAL (LABORATORY) SAMPLES

178. Each Final (Laboratory) Sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged in shipping.

179. The container should be sealed so that unauthorized opening is detectable.

180. The container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage.

181. Replicate portions of the Final (Laboratory) Sample which may be retained as required by national 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.

7. RECORDS

182. Each Primary or Bulk Sample and each Final (Laboratory) should be correctly identified by a record with the type of sample, its origin (e.g., country, state, or town), its location of collection, date of sampling, and additional information useful to the analyst or to regulatory officials for follow-up action if necessary.

8. DEPARTURE FROM RECOMMENDED SAMPLING PROCEDURES

183. If there is a departure from recommended sampling procedures, records accompanying the sample should fully describe procedures actually followed.

9. SAMPLING INSTRUCTIONS

9.1 LIQUID OR STRAINED HONEY

184. [If sample is free from granulation, mix thoroughly by stirring or shaking; if granulated, place closed container in water-bath without submerging, and heat 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 sample liquefies. 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.]

185. Collect 250 ml of liquid or strained honey.

9.2 COMB HONEY

186. 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 565-1983)[4]. When portions of comb or wax pass through sieve, heat samples as in paragraph 9.1 and strain through cheesecloth. If honey is granulated in comb, heat until wax is liquefied; stir, cool and remove wax.

187. Collect 250 ml of liquid honey.

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

GENERAL CONSIDERATIONS ON ANALYTICAL METHODS FOR RESIDUE CONTROL

1. INTRODUCTION

188. Analytical methods used to determine compliance with 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 within the terms of reference of this Codex Committee. 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.

189. 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.

190. Suitably validated methods are not always available for all possible combinations of veterinary drug residues and foods within the terms of reference of the CCRVDF. 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.

2. INTEGRATING ANALYTICAL METHODS FOR RESIDUE CONTROL

191. 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 maximum residue limit (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, the confirmed presence of residues at any concentration in a food may result in regulatory action.

192. 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. The CCRVDF has designated three categories of methods for use in regulatory programmes for the control of veterinary drug residues in foods. Completion of a full collaborative study[5] is not a requirement for recognition of a method to be placed in one of these three categories.

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

193. Level III 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 Level III 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.

194. Level II 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.

195. Level I methods provide unequivocal confirmation of the identity of the residue and may also confirm the quantity present. Level I 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 Level I method does not provide quantitative information, the quantification result of the original Level II method should be verified by analysis of replicate test portions using the original quantitative method or a suitably validated alternative quantitative method.

196. 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.

197. Samples which test “positive” with the Level III 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 Level III method, but typically Level II and/or Level I 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 Chapter “*Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods*”.

3 CONSIDERATIONS FOR SELECTION AND VALIDATION OF ANALYTICAL METHODS

3.1 IDENTIFICATION OF METHODS REQUIREMENTS

3.1.1 Method scope

198. 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.

3.1.2 Marker residue

199. 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.

3.1.3 Target Tissue

200. 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.

3.2 IMPLEMENTING CODEX ALIMENTARIUS COMMISSION GUIDELINES

201. The Codex Alimentarius Commission has issued a guideline for laboratories involved in the import/export testing of foods[6] 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[7];

b. participate in appropriate proficiency testing schemes designed and conducted in accordance with the International Harmonized Protocol for Proficiency Testing of (Chemical) Analytical Laboratories[8];

c. become accredited according to ISO/IEC-17025:2005 General requirements for the competence of calibration and testing laboratories[9];and

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

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

7 Thompson, M. and Wood, R. 1995. Harmonized Guidelines for Internal Quality Control in Analytical Chemistry Laboratories. Pure & Appl. Chem. 67: 649-666.

8 Thompson, M. and Wood, R. 1993. International Harmonized Protocol for Proficiency Testing of (Chemical) Analytical Laboratories. Pure & Appl. Chem. 65: 2132-2144.

9 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 superceded by ISO/IEC-17025: General requirements for the competence of calibration and testing laboratories. International Organization for Standardization, Geneva (1999).

202. 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.

3.3 METHOD VALIDATION AND FITNESS FOR PURPOSE

203. 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.

204. 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.

205. 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)[5.] 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 level of statistical confidence obtained from the results of a collaborative study.

206. 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.

207. 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.

208. 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 validation studies conducted within their own laboratory to characterize the method performance.

3.4 SINGLE LABORATORY VALIDATION – THE CRITERIA APPROACH

209. 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[10]. Requirements for the use of single-laboratory validation of methods for Codex purposes have also been considered by the Codex Committee on Methods of Analysis and Sampling[11]. The Procedural Manual[12] 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 (1999) Standard or with the Principles of Good Laboratory Practice.

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10 Thompson, M., Ellison, S.L.R. & Wood, R. (2002)) Harmonized Guidelines for Single-Laboratory Validation of Methods of Analysis. *Pure & Appl. Chem*. **74**: 835-852.

11 CX/MAS 02/11.

12 FAO/WHO. 2004. Codex Alimentarius Commission Procedural Manual, 14th Ed., Food and Agriculture Organization of the United Nations, Rome.

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

i) regular participation in proficiency schemes, where available;

ii) calibration using certified reference materials, where applicable;

iii) recovery studies performed at the expected concentration of the analytes;

iv) verification of result with other validated method where available.

210. 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, such as the European Commission[13].

[13] Commission Decision 2002/657/EC, implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results, *Official Journal of the European Communities, L221/8,* August 17, 2002.

ATTRIBUTES OF ANALYTICAL METHODS FOR RESIDUES OF VETERINARY DRUGS IN FOODS

1. INTRODUCTION

211. 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. Chapter "*General Considerations of Analytical Methods for Residue Control*", 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 Level I, Level II and Level III methods) defined by CCRVDF 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. (Note: This Part contains numerous definitions. The CCRVDF has attempted to harmonize these definitions with those provided in the "Analytical Terminology for Codex Use" in the Procedural Manual and those used by the Joint FAO/WHO Expert Committee on Food Additives in assessment of veterinary drug residues and analytical methods.)

2 METHOD DEVELOPMENT CONSIDERATIONS

212. 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[9]. 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.

213. 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.

3 ANALYTICAL PERFORMANCE CHARACTERISTICS

3.1 PERFORMANCE CHARACTERISTICS OF SCREENING (LEVEL III) METHODS

214. 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.

215. 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.

216. 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 Level III 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 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.

217. 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].

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

3.2 PERFORMANCE CHARACTERISTICS FOR QUANTITATIVE (LEVEL II) METHODS

218. *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 Level II 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.

219. 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

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

220. CCRVDF has 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 1, 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 1. Performance criteria which should be met by methods suitable for use as quantitative (Level II) 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

[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, November 8-11, 1999. Report published on the website of the International Atomic Energy Agency (IAEA). http://www.iaea.org/trc/pest-qa_val2.htm (accessed 2005/05/20).

221. 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 that 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.

222. *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. This has been addressed by some regulatory authorities in the establishment of requirements for the performance of regulatory methods of analysis[14]. 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] .

223. *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 as repeatability should be determined from experiments conducted on different days, using a minimum of six different tissue pools, different reagent batches(and 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.

224. 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 level of performance in the laboratory where it was developed, it cannot be expected to do any better in other laboratories.

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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 Appl. Chem.*, **71**:. 337 – 348.

225. 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 each of 0.5x, 1.0x and 2.0x the MRLVD (use of 6 different sources of blank materials is recommended).

226. 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.

227. 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.

228. 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 1 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*, 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 lowest calibrated level (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]. CCMAS has recently recommended replacing the term "*determination limit" with quantification limit* This is defined as 6 or 10 times the standard deviation of the mean value signal of a field blank, consistent with the definitions of LOQ.

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[17] Miller, J.C., & Miller, J.N. (1993) Statistics for Analytical Chemistry, 3rd Edition, Ellis Horwood Ltd., Chichester.

3.3 PERFORMANCE CHARACTERISTICS FOR CONFIRMATORY (LEVEL I) METHODS

229. *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 Level I methods are based.

230. 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] and several regulatory authorities [14,19], are given in Table 2.

Table 2: 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 %
< 10%	> 50 %	> 50 %

231. 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.

232. 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.

233. 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:

- thin layer chromatography,
- element-specific gas-liquid chromatography and accompanying detection systems,
- formation of characteristic derivatives followed by additional chromatography, or
- determining compound specific relative retention times using several chromatographic systems of differing polarity.

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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

19 Guidance for Industry: Mass Spectrometry for Confirmation of the Identity of Animal Drug Residues. U.S. Food & Drug Administration. http://www.fda.gov/cvm/guidance/guide118.doc (Accessed January 20, 2005)

234. 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[20]. 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 3.

Table 3. Examples of detection methods suitable for the confirmatory analysis of substances, as recommended by the Miskolc Consultation[16]

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.

235. Although Level I 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 Level I method, if it has sufficient sensitivity and precision.

3.4 GENERAL PERFORMANCE CHARACTERISTICS FOR METHODS FOR USE IN A REGULATORY CONTROL PROGRAMME

236. 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.

237. *Ruggedness* testing should be conducted using the standard factorial design approach to determine any critical control points[21]. 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 derivatization procedures than are used in the quantitative method).

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20 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.

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

238. *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 analyzed 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 analyzed 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.

239. *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.

4 METHOD DEVELOPMENT AND VALIDATION CONSIDERATIONS FOR RESIDUE CONTROL METHODS

4.1 SELECTION OF APPROPRIATE TEST MATERIAL FOR VALIDATION

240. 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 validation7 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.

241. 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 by CCRVDF.

242. 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 level II or III 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.

243. 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 analyzing residue control samples.

4.2 MEASUREMENT UNCERTAINTY

244. Laboratories should provide their clients on request with information on the measurement uncertainty associated with the quantitative results produced by each quantitative method[4]. This requires a review of the method to determine the potential error that may be introduced at each step of the method, from preparation of standards, selection and weighing of test portions, through each step in the analysis to final measurement. The more complex and involved the method, the more difficult this becomes to accomplish. An alternative approach uses method validation and/or on-going QC data generated in the laboratory to estimate the measurement uncertainty. Guidance on estimation of measurement uncertainty is being developed by IUPAC and has been published by other independent scientific bodies.[22]

4.3 USE OF INTERNAL STANDARDS

245. 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.

4.4 ENVIRONMENTAL CONSIDERATIONS

246. When residue control methods that 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.

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22 EURACHEM/CITAC Guide to Quantifying Measurement Uncertainty in Analytical Measurement, http://www.measurementuncertainty.org/mu/guide/index.html, accessed May 20, 2005.

4.5 CHOICE OF VALIDATION MODEL

247. 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. As a minimum, CCRVDF previously recommended that three laboratories expected to use these methods should develop performance characteristics for residue control, including analytical variability, and obtain statistically acceptable agreement on the same samples divided among the testing laboratories. Such an approach is still recommended, whenever possible. However it is also recognized that the rapid changes in technology and the ever-increasing range of compounds which may be included in a residue control programme require from a practical approach that laboratories focus first on internal validation of methods to meet the time constraints. 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.

248. 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 randomized 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[10,] 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.

4.6 QUALITY CONTROL AND QUALITY ASSURANCE

249. 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[6].

Appendix VIII

PROPOSED DRAFT
RISK ANALYSIS PRINCIPLES APPLIED BY THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

(for inclusion in the Codex Procedural Manual)

1. PURPOSE – SCOPE

1. The purpose of this document is to specify Risk Analysis Principlesapplied by the Codex Committee on Residues of Veterinary Drugs in Foods.

2. PARTIES INVOLVED

2. The *Working Principles for Risk Analysis for application in the framework of the Codex Alimentarius*[1] has defined the responsibilities of the various parties involved. The responsibility for providing advice on risk management concerning residues of veterinary drugs lies with the Codex Alimentarius Commission (CAC) and its subsidiary body, the Codex Committee on Residues of Veterinary Drugs in Foods (CCRDVF), while the responsibility for risk assessment lies primarily with the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3. According to its mandate, the responsibilities of CCRVDF regarding veterinary drug residues in food are:

(a) to determine priorities for the consideration of residues of veterinary drugs in foods;

(b) to recommend MRLs for such veterinary drugs;

(c) to develop codes of practice as may be required;

(d) to consider whether available methods of sampling and analysis for the determination of veterinary drug residues in foods.

4. CCRVDF shall base its risk management recommendations to the Codex Alimentarius Commission (CAC) on JECFA's risk assessments of veterinary drugs in relation to proposed MRLs.

5. CCRVDF is primarily responsible for recommending risk management proposals for adoption by the Codex Alimentarius Commission (CAC).

6. JECFA is primarily responsible for providing independent scientific advice, the risk assessment, upon which CCRVDF base their risk management decisions. It assists the CCRVDF by evaluating the available scientific data on the veterinary drug prioritised by CCRVDF. JECFA also provides advice directly to FAO and WHO and to Member governments.

7. Scientific experts from JECFA are selected in a transparent manner by FAO and WHO under their rules for expert committees on the basis of the competence, expertise, experience in the evaluation of compounds used as veterinary drugs and their independence with regard to the interests involved, taking into account geographical representation where possible.

3. RISK MANAGEMENT IN CCRVDF

8. Risk management should follow a structured approach including:

- preliminary risk management activities;
- evaluation of risk management options; and
- monitoring and review of decisions taken.

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1 Codex Procedural Manual, 15th Edition page 101 (English version).

9. The decisions should be based on risk assessment, and take into account, where appropriate, other legitimate factors relevant for the health protection of consumers and for fair practices in food trade, in accordance with the *Criteria for the Consideration of the Other Factors Referred to in the Second Statement of Principles*[2].

3.1 PRELIMINARY RISK MANAGEMENT ACTIVITIES

10. This first phase of risk management covers:

- Establishment of risk assessment policy for the conduct of the risk assessments;
- Identification of a food safety problem;
- Establishment of a preliminary risk profile;
- Ranking of the hazard for risk assessment and risk management priority;
- Commissioning of the risk assessment; and
- Consideration of the result of the risk assessment.

3.1.1 Risk Assessment Policy for the Conduct of the Risk Assessment

11. The responsibilities of CCRVDF and JECFA and their interactions along with core principles and expectations of JECFA evaluations are provided in *Risk Assessment Policy for the Setting of MRLs in Food*, established by the Codex alimentarius Commission.

3.1.2 Identification of a Food Safety Problem (establishment of the priority list)

12. CCRVDF identifies, with the assistance of Members, the veterinary drugs that may pose a consumer safety problem and/or have a potential adverse impact on international trade. CCRVDF establishes a priority list for assessment by JECFA.

13. In order to appear on the priority list of veterinary drugs for the establishment of a maximum residue limit (MRL), the proposed veterinary drug shall meet some or all of the following criteria:

- A Member has proposed the compound for evaluation;
- A Member has established good veterinary practices with regard to the compound;
- The compound has the potential to cause public health and/or international trade problems;
- It is available as a commercial product; and
- There is a commitment that a dossier will be made available.

14. The CCRVDF takes into account the protection of confidential information in accordance with WTO rules article 39, and makes every effort to encourage the willingness of sponsors to provide data for JECFA assessment.

3.1.3 Establishment of a Preliminary Risk Profile

15. Member(s) request(s) the inclusion of a veterinary drug on the priority list. The available information for evaluating the request shall be provided either directly by the Member(s) or by the sponsor. A preliminary risk profile shall be developed by the Member(s) making the request, using the template presented in the ANNEX.

16. The CCRVDF considers the preliminary risk profile and makes a decision on whether or not to include the veterinary drug in the priority list.

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2 Codex Procedural Manual, 15th Edition page 159 (English version)

3.1.4 Ranking of the Hazard for Risk Assessment and Risk Management Priority

17. The CCRVDF establishes an ad-hoc Working Group open to all its Members and observers, to make recommendations on the veterinary drugs to include into (or to remove from) the priority list of veterinary drugs for the JECFA assessment. The CCRVDF considers these recommendations before agreeing on the priority list. taking into account pending issues such as temporary Acceptable Daily Intakes (ADIs) and/or MRLs. In its report, the CCRVDF shall specify the reasons for its choice and the criteria used to establish the order of priority.

18. Prior to development of MRLs for new veterinary drugs not previously evaluated by JECFA, a proposal for this work shall be sent to the Codex Alimentarius Commission with a request for approval as new work in accordance with the Procedures for the Elaboration of Codex Standards and Related Texts.[3]

3.1.5 Commissioning of the Risk Assessment

19. After approval by the Codex Alimentarius Commission of the priority list of veterinary drugs as new work, the CCRVDF forwards it to the JECFA with the qualitative preliminary risk profile as well as specific guidance on the CCRVDF risk assessment request. JECFA, WHO and FAO experts then proceed with the assessment of risks related to these veterinary drugs, based on the dossier provided and/or all other available scientific information.

3.1.6 Consideration of the Result of the Risk Assessment

20. When the JECFA risk assessment is completed, a detailed report is prepared for the subsequent session of the CCRVDF for consideration. This report shall clearly indicate the choices made during the risk assessment with respect to scientific uncertainties and the level of confidence in the studies provided.

21. When the data are insufficient, JECFA may recommend temporary MRL on the basis of a temporary ADI using additional safety considerations[4]. If JECFA cannot propose an ADI and/or MRLs due to lack of data, its report should clearly indicate the gaps and a timeframe in which data should be submitted, in order to allow Members to make an appropriate risk management decision.

22. The JECFA assessment reports related to the concerned veterinary drugs should be made available in sufficient time prior to a CCRVDF meeting to allow for careful consideration by Members. If this is, in exceptional cases not possible, a provisional report should be made available.

23. The JECFA should, if necessary, propose different risk management options. In consequence, JECFA should present, in its report, different risk management options for CCRVDF to consider. The reporting format should clearly distinguish between the risk assessment and the evaluation of the risk management options.

24. The CCRVDF may ask JECFA any additional explanation.

25. Reasons, discussions and conclusions (or the absence thereof) on risk assessment should be clearly documented, in JECFA reports, for each option reviewed. The risk management decision taken by CCRVDF (or the absence thereof) should also be fully documented.

3.2 EVALUATION OF RISK MANAGEMENT OPTIONS

26. The CCRVDF shall proceed with a critical evaluation of the JECFA proposals on MRLs and may consider other legitimate factors relevant for health protection and fair trade practices in the framework of the risk analysis. According to the 2nd statement of principle, the criteria for the consideration of other factors should be taken into account. These other legitimate factors are those agreed during the 12th session of the CCRVDF[5] and subsequent amendments made by this Committee.

27. The CCRVDF either recommends the MRLs as proposed by JECFA, modifies them in consideration of other legitimate factors, considers other measures or asks JECFA for reconsideration of the residue evaluation for the veterinary drug in question.

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3 Codex Procedural Manual, 15th Edition pages 19-30 (English version).

4 Codex Procedural Manual, 15th Edition page 45 (English version).

5 See Report of the 12th session of the CCRVDF ALINORM 01/31 para 11.

28. Particular attention should be given to availibility of analytical methods used for residue detection.

3.3 MONITORING AND REVIEW OF THE DECISIONS TAKEN

29. Members may ask for the review of decisions taken by the Codex Alimentarius Commission. To this end, veterinary drugs should be proposed for inclusion in the priority list. In particular, review of decisions may be necessary if they pose difficulties in the application of the *Guidelines for the Establishment of a Regulatory Program for the Control of Veterinary Drug Residues in Foods.*

30. CCRVDF may request JECFA to review any new scientific knowledge and other information relevant to risk assessment and concerning decisions already taken, including the established MRLs.

31. The risk assessment policy for MRL shall be reconsidered based on new issues and experience with the risk analysis of veterinary drugs. To this end, interaction with JECFA is essential. A review may be undertaken of the veterinary drugs appearing on prior JECFA agendas for which no ADI or MRL has been recommended.

4. RISK COMMUNICATION IN THE CONTEXT OF RISK MANAGEMENT

32. In accordance with the *Working Principles for Risk Analysis for Application in the Framework of the Codex Alimentarius*[6], the CCRVDF, in cooperation with JECFA, shall ensure that the risk analysis process is fully transparent and thoroughly documented and that results are made available in a timely manner to Members. The CCRVDF recognises that communication between risk assessors and risk managers is critical to the success of risk analysis activities.

33. In order to ensure the transparency of the assessment process in JECFA, the CCRVDF provides comments on the guidelines related to assessment procedures being drafted or published by JECFA.

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6 Codex Procedural Manual, 15th Edition page 161 (English version).

ANNEX

TEMPLATE FOR INFORMATION NECESSARY FOR PRIORITIZATION BY CCRVDF

Administrative information

1. Member(s) submitting the request for inclusion
2. Veterinary drug names
3. Trade names
4. Chemical names
5. Names and addresses of basic producers

Purpose, scope and rationale

6. Identification of the food safety issue (residue hazard)
7. Assessment against the criteria for the inclusion on the priority list

Risk profile elements

8. Justification for use
9. Veterinary use pattern
10. Commodities for which Codex MRLs are required

Risk assessment needs and questions for the risk assessors

11. Identify the feasibility that such an evaluation can be carried out in a reasonable framework
12. Specific request to risk assessors

Available information[7]

13. Countries where the veterinary drugs is registered
14. National/Regional MRLs or any other applicable tolerances
15. List of data (pharmacology, toxicology, metabolism, residue depletion, analytical methodos) available

Timetable

16. Date when data could be submitted to JECFA

[7] When preparing a preliminary risk profile, Member(s) should take into account the updated data requirement, to enable evaluation of a veterinary drug for the establishment of an ADI and MRLs, published by JECFA.

Appendix IX

PROPOSED DRAFT
RISK ASSESSMENT POLICY FOR THE SETTING OF MRLS IN FOOD

(for inclusion in the Codex Procedural Manual)

Role of JECFA

1. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) is an independent scientific expert body convened by both Director Generals of FAO and WHO according to the rules of both organizations, charged with the task to provide scientific advice on veterinary drug residues in food.

2. This annex applies to the work of JECFA in the context of Codex and in particular as it relates to advice requests from CCRVDF

(a) JECFA provides CCRVDF with science-based risk assessments conducted in accordance with the *Statements of principles relating to the role of food safety risk assessment*[1] and incorporating the four steps of risk assessment. JECFA should continue to use its risk assessment process for establishing ADIs and proposing MRLs.

(b) JECFA should take into account all available scientific data to establish its risk assessment. It should use available quantitative information to the greatest extent possible and also qualitative information.

(c) Constraints, uncertainties and assumptions that have an impact on the risk assessment need be clearly communicated by JECFA.

(d) JECFA should provide CCRVDF with information on the applicability, public health consequences and any constraints of the risk assessment to the general population and to particular sub-populations and, as far as possible, should identify potential risks to specific group of populations of potentially enhanced vulnerability (e.g. children).

(e) Risk assessment should be based on realistic exposure scenarios.

(f) When the veterinary drug is used both in veterinary medicine and as a pesticide, a harmonised approach between JECFA and JMPR should be followed.

(g) MRLs, that are compatible with the ADI, should be set for all species based on appropriate consumption figures. When requested by CCRVDF, extension of MRLs between species will be considered if appropriate data are available.

Data Protection

3. Considering the importance of intellectual property in the context of data submission for scientific evaluation, JECFA has established procedures to cover the confidentiality of certain data submitted. These procedures enable the sponsor to declare which data is to be considered as confidential. The procedure includes a formal consultation with the sponsor.

Expression of risk assessment results in terms of MRLs

4. MRLs have to be established for target animal tissues (e.g. muscle, fat, or fat and skin, kidney, liver), and specific food commodities (e.g. eggs, milk, honey) originating from the target animals species to which a veterinary drug can be administered according to good veterinary practice.

5. However, if residue levels in various target tissues are very different, JECFA is requested to consider MRLs for a minimum of two. In this case, the establishment of MRLs for muscle or fat is preferred to enable the control of the safety of carcasses moving in international trade.

6. When the calculation of MRLs to be compatible with the ADI may be associated with a lengthy withdrawal period, JECFA should clearly describe the situation in its report.

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1 Codex Procedural Manual 15th Edition page 161 (English version).

Appendix X

COMPENDIUM OF METHODS OF ANALYSIS IDENTIFIED AS SUITABLE TO SUPPORT CODEX MRLs

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Abamectin	Abamectin B_{1a}	Yes	LC	liver	cattle	100	5	45th JECFA	FAO Food & Nutrition Paper 41/8	full recommendation
				kidney	cattle	50	5			
				fat	cattle	100	5			
Albendazole	2-amino-benzimidazole, as parent drug equivalents	Yes	LC	liver	cattle	5000		3-lab trial, data provided to CCRVDF	*Chemistry Laboratory Guidebook*. United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C.	full recommendation
		Yes	LC	milk	cattle	100		info provided to 13th Meeting, CCRVDF	Contact: AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France	provisional recommendation
		Yes	LC	liver	sheep	5000		3-lab trial,data provided to CCRVDF	*Chemistry Laboratory Guidebook*. United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C.	full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Azaperone	sum of azaperone and azaperol	Yes	LC	liver	pig	100	2	Data provided to CCRVDF by U.K.	Rose, M.D., and Shearer, G. (1992). *J. Chromatogr*. 624: 471-477	provisional recommendation
		Yes	LC	kidney	pig	100	2 (ref 1); 2.5 (ref. 2)	Data provided to CCRVDF by Netherlands (1, 2) and U.K. (3)	**1.** Keukens, H.J., and Aerts, M.M.L. (1989). *J. Chromatogr*. 464: 149-161. **2.** Van Ginkel, L.A., Schwillens, P.L.W.J., and Olling, M. (1989). *Anal. Chim. Acta* 225: 137- 146. **3.** Rose, M.D., and Shearer, G. (1992). *J. Chromatogr*. 624: 471-477.	provisional recommendation
				muscle	pig	60		info provided to 13th Meeting, CCRVDF	Contact: AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France	provisional recommendation
Benzylpenicillin	benzylpenicillin	Yes	LC	liver	All species	50	5	Original data submitted by Canada, confirmed by UK, Brazil, data provided to CCRVDF	Boison, J.O., Salisbury, C.D.C., Chan, W., and MacNeil, J.D. (1991). *J. Assoc. Offic. Anal. Chem*. 74: 497-501.	full recommendation
				kidney	All species	50	5			
				muscle	All species	50	5			
		Yes	GC	milk		4		Method provided to CCRVDF	Compilation of methods proposed as regulatory methods or used in regulatory programs in European Union, prepared for Working Group by France: Method for penicillins in milk by capillary gas	provisional recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									chromatography from the "Collection of official methods under Article 35 of the German Federal Foods Act"; see Meetschen, U., & Petz, M. (1991) *Z. Lebensm. Unters. Forsch*., 193: 337-343; see also *Bundesgesundhbl*. 36: 118-121 (1993).	
				kidney muscle fat milk						
Carazol	Carazol	Yes	LC	liver	pig	25	2	Data provided to CCRVDF by U.K. (1) and Germany (2)	**1.** Rose, M.D., and Shearer, G. (1992). *J. Chromatogr*. 624: 471-477. **2.** Rudolph, M., and Steinhart, H. (1987). *J. Chromatogr*. 392: 371-378.	provisional recommendation
				kidney		25	0.3		**1.** Keukens, H.J., and Aerts, M.M.L. (1989). J. Chromatogr. 464: 149-161. **2.** Rose, M.D., and Shearer, G. (1992). J. Chromatogr. 624: 471-477. 3. Rudolph, M., and Steinhart, H. (1987). *A second laboratory*	provisional recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									evaluation of this method was provided by the UK to the 12th CCRVDF. J. Chromatogr. 392: 371-378. **4.** Vogelsgang, J. (1989). *Deutsch. Lebensm.Rndsch.* 85: 251-258.	
Ceftiofur	desfuroylceftiofur acetamide	Yes	LC	liver	cattle	2000	100	Data provided to 12th Meeting, CCRVDF, and 47th JECFA	Report of 12th Meeting, CCRVDF; FAO Food & Nutrition Paper 41/8	provisional recommendation
				kidney		6000	50		FAO Food & Nutrition Paper 41/8; see also Hornish, R.E., Hamlow, P.J., & Brown, S.A.. (2003) *J. AOAC Int*. 86: 30-38 for report of 4-laboratory trial of method for analysis of kidney and muscle (cattle and pig) and milk.	
				muscle		1000	50	data provided to CCRVDF and to 47th JECFA		full recommendation
				fat		2000		Data provided to 12th Meeting, CCRVDF, and 47th JECFA	Report of 12th Meeting, CCRVDF; FAO Food & Nutrition Paper 41/8; method LOD given as 50 µg/kg, LOQ not reported.	provisional recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
				milk		100	50	data provided to CCRVDF and to 47th JECFA	FAO Food & Nutrition Paper 41/8; see also Hornish, R.E., Hamlow, P.J., & Brown, S.A.. 2003. *J. AOAC Int*. 86: 30-38 for report of 4-laboratory trial of method for analysis of kidney and muscle (cattle and pig) and milk.	full recommendation
				liver	pig	2000	1000	Data provided to 12th Meeting, CCRVDF, and47th JECFA	Report of 12th Meeting, CCRVDF; FAO Food & Nutrition Paper 41/8; method LOD given as 50 µg/kg, LOQ not reported. UK reported method evaluation to 12th CCRVDF indicating acceptable accuracy and precision from 1000 to 4000 µg/kg from pig liver, but recoveries in range of 60%	provisional recommendation
				kidney		6000	100	data provided to CCRVDF and to 47th JECFA	FAO Food & Nutrition Paper 41/8; see also Hornish, R.E., Hamlow, P.J., & Brown, S.A.. 2003. *J. AOAC Int*. 86: 30-38 for report of 4-laboratory trial of method for analysis of kidney and	full recommendation
				muscle		1000	30			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									muscle (cattle and pig) and milk.	
				fat		2000		Data provided to 12th Meeting, CCRVDF, and 47th JECFA	Report of 12th Meeting, CCRVDF; FAO Food & Nutrition Paper 41/8; method LOD given as 50 µg/kg, LOQ not reported.	provisional recommendation
Chlortetracycline, oxytetracycline, tetracycline	Parent drugs, singly or in combination	Yes	LC	liver	cattle	600	50-100	data provided to CCRVDF	AOAC 995.09 extension (Canada)	full recommendation
				kidney		1200	200-250	**1.** AOAC collaborative study, data provided to CCRVDF; **2.** 6-lab method trial, data provided to CCRVDF by Poland	**1.** MacNeil JD, Martz VK, Korsrud GO, Salisbury CDC, Oka H, Epstein RL, Barnes CJ. (1996) *J. AOAC Int.* 79: 405 - 417. See also AOAC Official Method 995.09: Chlortetracycline, Oxytetracycline and Tetracycline in Edible Animal Tissues. (1996). *AOAC Official Methods of Analysis, 16th edition, Supplement March 1996.* AOAC International, Gaithersburg, MD. **2.** Posyniak, A. Zmudzki, J., Ellis, R.L., Semeniuk, S., & Niedzielska, J.	
				muscle		200	100-200			full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									(1999) J. AOAC Int. 82: 862-865.	
		Yes	LC	milk		100	15	AOAC collaborative study, data provided to CCRVDF	Carson, MC, & Breslyn, W. (1996) *J. AOAC Int*. 79: 29 - 42. See also AOAC Official Method 995.04 : Multiple Tetracycline Residues in Milk. (1996). AOAC Official Methods of Analysis, 16th edition, Supplement March 1996. AOAC International, Gaithersburg, MD.	full recommendation
				liver	sheep	600				
				kidney		1200				
				muscle		200	100-200			provisional recommendation
				milk		100				
				liver	pig	600		data provided to CCRVDF	AOAC 995.09 extension (Canada)	full recommendation
				kidney		1200	200 - 600	AOAC collaborative study, data provided to CCRVDF	MacNeil JD, Martz VK, Korsrud GO, Salisbury CDC, Oka H, Epstein RL, Barnes CJ. (1996) *J. AOAC Int.* 79: 405 - 417. See also AOAC Official Method 995.09: Chlortetracycline,	
				muscle		200	100-200			full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									Oxytetracycline and Tetracycline in Edible Animal Tissues. (1996). AOAC Official Methods of Analysis, 16th edition, Supplement March 1996. AOAC International, Gaithersburg, MD.	
				liver	poultry	600				
				kidney		1200				
				muscle		200				provisional recommendation
				eggs		400				
		Yes		muscle	giant prawn	100		JECFA review; Data provided to CCRVDF	AOAC 995.09 by extension (validation data provided by Thailand to JECFA and CCRVDF); additional data provided by Thailand to 16th CCRVDF	full recommendation
	OTC only			muscle	fish	200		58th JECFA; Data provided to CCRVDF	FAO Food & Nutrition Paper 41/14; additional data provided by Canada to 16th CCRVDF	full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Clenbuterol	Clenbuterol	Yes	GC/MS	liver	cattle	0.6		47th JECFA	FAO Food & Nutrition Paper 41/9	
				kidney		0.6				
				muscle		0.2				
				fat		0.2				
				milk		0.05				
				liver	horse	0.6				
				kidney		0.6				
				muscle		0.2				
				fat		0.2				full recommendation
Closantel	Closantel	Yes		liver	cattle	1000		info provided to 13th Meeting, CCRVDF	Contact: AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France	provisional recommendation
		Yes	LC	muscle		1000			Michiels, M., Meuldermans, W., and Heykants, J. (1987). *Drug Metab. Rev.* 18: 235-251.	full recommendation
		Yes	LC	muscle	sheep	1500			Michiels, M., Meuldermans, W., and Heykants, J. (1987). *Drug Metab. Rev.* 18: 235-251.	full recommendation
Cyfluthrin	Cyfluthrin	Yes	GC	liver	cattle	20	10	48th JECFA	FAO Food & Nutrition Paper 41/10	full recommendation
				kidney		20	10			
				muscle		20	10			
				fat		200	10			
				milk		40	5			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Cyhalothrin	Cyhalothrin	Yes	GC	liver	cattle	20	10	54th JECFA	FAO Food & Nutrition Paper 41/13	full recommendation
				kidney		20	10			
				muscle		20	10			
				fat		400	10			
				milk		30	10			
				liver	sheep	50	50	54th JECFA, revised by 62nd JECFA		
				kidney		20	10	54th JECFA		
				muscle		20	10			
				fat		400	10			
				liver	pig	20	10			
				kidney		20	10			
				muscle		20	10			
				fat		400	10			
Cypermethrin	Cypermethrin	Yes	GC	liver	sheep	50	10	58th JECFA; revised by 62nd JECFA	FAO Food & Nutrition Papers 41/14 & 41/16	full recommendation
				kidney		50	10			
				muscle		50	10			
				fat		100	10			
α-Cypermethrin	α-Cypermethrin	Yes	GC	liver	cattle	50	10	58th JECFA; revised by 62nd JECFA	FAO Food & Nutrition Papers 41/14 & 41/16	full recommendation
				kidney		50	10			
				muscle		50	10			
				fat		1000	100			
				milk		100	10			
				liver	sheep	50	10			
				kidney		50	10			
				muscle		50	10			
				fat		1000	100			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Danofloxacin	Danofloxacin	Yes	LC	liver	cattle	400	10	48th JECFA; info also provided to 13th CCRVDF by France.	FAO Food & Nutrition Paper 41/10; see also Report of 12th & 13th Meetings, CCRVDF. Contact for method provided to CCRVDF: AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France	full recommendation
				kidney		400	10			
				muscle		200	10			
				fat		100	10			
				liver	pig	50	10			
				kidney		200	10			
				muscle		100	10			
				fat		100	10			
				liver	chicken	400	10			
				kidney		400	10			
				muscle		200	10			
				fat		100	10			
Deltamethrin	Deltamethrin	Yes	GC	liver	cattle	50	15	52nd JECFA	FAO Food & Nutrition Paper 41/12	full recommendation
				kidney		50	15			
				muscle		30	15			
				fat		500	45			
				milk		30	15			
		Yes	GC	liver	chicken	50	15	52nd JECFA	FAO Food & Nutrition Paper 41/12	full recommendation
				kidney		50				
				muscle		30	15			
				fat		500	45			
				eggs		30	15			
				muscle	salmon	30	2			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Diclazuril	Diclazuril	Yes	GC	liver	sheep	3000	10	45th JECFA	FAO Food & Nutrition Paper 41/8	full recommendation
				kidney		2000	10			
				muscle		500	10			
				fat		1000	10			
			GC, LC	liver	poultry	3000	10, 50			
				kidney		2000	10, 50			
				muscle		500	10, 50			
				fat		1000	10, 50			
			LC	liver	rabbit	3000	50			
				kidney		2000	50			
				muscle		500	50			
				fat		1000	50			
Dicyclanil	Dicyclanil	Yes	LC	liver	sheep	125	10	60th JECFA	FAO Food & Nutrition Paper 41/15	full recommendation
				kidney		125	10			
				muscle		150	10			
				fat		200	10			
Dihydrostreptomycin, streptomycin	Dihydrostreptomycin, streptomycin	Yes	LC	liver	cattle	600	200 - 300	58th JECFA; info provided to CCRVDF	FAO Food & Nutrition Paper 41/14; see also Gerhardt, G.C., Salisbury, C.D.C., & MacNeil, J.D. (1994) *J. AOAC Int.* 77: 334-337; data provided to CCRVDF by Canada, 2nd laboratory verification of performance reported by UK. For additional methods, contact AFSSA-LERMVD,	full recommendation
				kidney		1000	200 - 300			
				muscle		600	200 - 300			
				fat		600	200 - 300			
				milk		200	50			
				liver	pig	600	200 - 300			
				kidney		1000	200 - 300			
				muscle		600	200 - 300			
				fat		600	200 - 300			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									Javene, BP090203-35302, Fougeres, France; Australian Government Analytical Laboratories, GPO Box 1844, Canberra ACT 2601, Australia.	
				liver	sheep	600	200 - 300			
				kidney		1000	200 - 300			
				muscle		600	200 - 300			
				fat		600	200 - 300			
				milk		200	50			
				liver	chicken	600	200 - 300			
				kidney		1000	200 - 300			
				muscle		600	200 - 300			
				fat		600	200 - 300			
Diminazene	Diminazene	Yes	LC	liver	cattle	12000	300	42nd JECFA	FAO Food & Nutrition Paper 41/6: info on method for cattle muscle, liver, kidney, fat and milk provided to 10th CCRVDF.	provisional recommendation
				kidney		6000	300			
				muscle		500	300			
				milk		150	150			
Doramectin	Doramectin	Yes	LC	liver	cattle	100	2.5	45th JECFA	FAO Food & Nutrition Paper 41/8	full recommendation
				kidney		30	2.5			
				muscle		10	2.5			
				fat		150	5			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
		Yes	LC	milk		15	3	62nd JECFA	FAO Food & Nutrition Paper 41/16	
				liver	pig	100	2.5	52nd JECFA	FAO Food & Nutrition Paper 41/12	
				kidney		30	2.5			
				muscle		5	2.5			
				fat		150	5			
									NOTE: For regulatory methods provided to CCRVDF contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France; Australian Government Analytical Laboratories, GPO Box 1844, Canberra ACT 2601, Australia.	
Eprinomectin	Eprinomectin	Yes	LC	liver	cattle	2000	2	50th JECFA	FAO Food & Nutrition Paper 41/11;	full recommendation
				kidney		300	2			
				muscle		100	2			
				fat		250	2			
				milk		20	1		NOTE: For regulatory method provided to CCRVDF contact Australian Government Analytical Laboratories, GPO Box 1844, Canberra ACT 2601, Australia.	

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Febantel, fenbendazole, oxfendazole	sum, expressed as oxfendazole sulfone equivalents	Yes	LC	liver	cattle	500	5	50th JECFA	FAO Food & Nutrition Paper 41/11	full recommendation
				kidney		100	5			
				muscle		100	5		See also Chemistry Laboratory Guidebook. United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C. (data provided to CCRVDF by United States). Additional contact for method for analysis of milk provided to CCRVDF: AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France.	
				fat		100	5			
				milk		100	5			
				liver	sheep	500	5			
				kidney		100	5			
				muscle		100	5			
				fat		100	5			
				milk		100	5			
				liver	pig	500	5			
				kidney		100	5			
				muscle		100	5			
				fat		100	5			
				liver	horse	500	5			
				kidney		100	5			
				muscle		100	5			
				fat		100	5			
				liver	goat	500	5			
				kidney		100	5			
				muscle		100	5			
				fat		100	5			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Fluazuron	Fluazuron	Yes	LC	liver	cattle	500	20	48th JECFA	FAO Food & Nutrition Paper 41/10	full recommendation
				kidney		500	20			
				muscle		200	20			
				fat		7000	10			
Flubendazole	Flubendazole	Yes	LC	liver	pig	10			Marti, A.M., Mooser, A.E., and Koch, H. (1990). *J. Chromatogr*. 498: 145-157; data provided to CCRVDF by Switzerland.	provisional recommendation
				muscle		10				
				liver	poultry	500				
				muscle		200				
				eggs		400				
Flumequine	Flumequine	Yes	LC	liver	cattle	500	50	48th JECFA	FAO Food & Nutrition Paper 41/10	provisional recommendation
		Yes	LC	kidney		3000	50	54th JECFA	FAO Food & Nutrition Paper 41/13	full recommendation
				muscle		500	50			
				fat		1000	25			
				liver	pig	500	50			
				kidney		3000	50			
				muscle		500	50			
				skin/fat		1000	50			
				liver	sheep	500	5		Additional supporting data provided to CCRVDF from compilation of methods proposed as regulatory methods or used in regulatory programs in European Union, prepared for Working Group by	
				kidney		3000	5			
				muscle		500	5			
				fat		1000	5			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									France.	
		Yes	LC	liver	chicken	500	100	48th JECFA	FAO Food & Nutrition Paper 41/10	provisional recommendation
		Yes	LC	kidney		3000	100	54th JECFA	FAO Food & Nutrition Paper 41/13	full recommendation
				muscle		500	25		additional info on regulatory method provided to CCRVDF, contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France.	
				fat		1000	50			
Gentamicin	Gentamicin	Yes	LC	liver	cattle	2000	200	50th JECFA	FAO Food & Nutrition Paper 41/11	full recommendation
				kidney		5000	1000			
				muscle		100	100			
				fat		100	100			
				milk		200	100			
				liver	pig	2000	200		NOTE: Additional info on regulatory method for pork kidney provided to CCRVDF, contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France. A 2nd laboratory evaluation of the method of McLaughlin, L. & Henion, J. (1994) *Biological Mass Spectrometry* 23: 417-429 for analysis of pig liver	
				kidney		5000	1000			
				muscle		100	100			
				fat		100	100			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									was reported to the 12th CCRVDF by the UK.	
Imidocarb	Imidocarb	Yes	LC	liver	cattle	2000	100	50th JECFA	FAO Food & Nutrition Paper 41/11; report notes that additional validation of method for tissues for species other than cattle required.	full recommendation
				kidney		1500	100			
				muscle		300	50			
				fat		50	50			
				milk		50	10			
Isometamidium	Isometamidium			liver	cattle	500		data provided to CCRVDF	Data provided on performance of drug sponsor's method.	provisional recommendation
				kidney		1000				
				muscle		100				
				fat		100				
				milk		100				
Ivermectin	Ivermectin B_{1a}	Yes	LC	liver	cattle	100	2	data provided to CCRVDF	***1.*** *Chemistry Laboratory Guidebook.* United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C. **2.** Tway, P.C., Wood, J.S., Jr., and Downing, G.V. (1981). *J. Agr. Food Chem.* 29: 1059-1063. **3.** Salisbury, C.D.C. (1993) J. AOAC Int. 76: 1149-1151, submitted by Canada, 2nd	full recommendation
				fat		40	2			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									laboratory confirming data on method performance provided by UK.	
		Yes	LC	milk		10		54th JECFA; info provided to 13th CCRVDF	Method considered by JECFA requires validation; info on regulatory method provided to CCRVDF by France, contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France.	provisional recommendation
		Yes	LC	liver	pig	15	2	data provided to CCRVDF	***1.*** *Chemistry Laboratory Guidebook*. United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C. **2.** Tway, P.C., Wood, J.S., Jr., and Downing, G.V. (1981). *J. Agr. Food Chem*. 29: 1059-1063. **3.** Salisbury, C.D.C. (1993) *J. AOAC Int*. 76: 1149-1151, submitted by Canada, 2nd laboratory confirming data provided by UK.	full recommendation
				fat		20	2			
				liver	sheep	15	2			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Levamisole	Levamisole	Yes	LC	liver	cattle	100		Data provided to CCRVDF by Denmark.	**1.** Danish National Food Agency, Method F40251. Data for cattle, pig and sheep liver only. NOTE: For additional regulatory method provided to CCRVDF contact Australian Government Analytical Laboratories, GPO Box 1844, Canberra ACT 2601, Australia.	provisional recommendation
		Yes	GC (Method 2)	liver	pig	100		Data provided to CCRVDF by Denmark and US.	**1.** Danish National Food Agency, Method F40251. Data for cattle, pig and sheep liver only. **2.** Chemistry Laboratory Guidebook. United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C. Data for pig liver only.	provisional recommendation
		Yes		liver	sheep	100		Data provided to CCRVDF by Denmark.	Danish National Food Agency, Method F40251. Data for cattle, pig and sheep liver only.	provisional recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Lincomycin	Lincomycin	Yes	GC/MS	milk	cattle	150	15	54th JECFA	FAO Food & Nutrition paper 41/13	full recommendation
				liver	pig	500	60			
				kidney		1500	60			
				muscle		200	17			
				fat		100	17			
				liver	chicken	500	17			
				kidney		500	17			
				muscle		200	17			
				fat		100	17			
Melengesterol acetate	Melengesterol acetate	Yes	LC/MS	liver	cattle	5	0.5	58th JECFA	FAO Food & Nutrition Paper 41/14	full recommendation
									NOTE: For regulatory method for cattle muscle and fat provided to CCRVDF contact RIVM, Community Reference Laboratory, Antonie van Leeuwenhoeklaan 9, 3720 BA Bilthoven, the Netherlands..	
				fat		8	0.5			
Moxidectin	Moxidectin	Yes	LC	liver	cattle	100	10	45th JECFA; data also provided to CCRVDF	FAO Food & Nutrition Paper 41/8	full recommendation
				kidney		50	10			
				muscle		20	10			
				fat		500	10		Information on regulatory methods for residues in liver of various species supplied to CCRVDF contact:	
				liver	sheep	100	10			
				kidney		50	10			
				muscle		50	10			
				fat		500	10			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
				liver	deer	100	2		AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France; Australian Government Analytical Laboratories, GPO Box 1844, Canberra ACT 2601, Australia.	
				kidney		50	2			
				muscle		20	2			
				fat		500	2			
Neomycin	Neomycin	Yes	LC	liver	cattle	500	100	52nd JECFA; data provided to CCRVDF	FAO Food & Nutrition Paper 41/12; Giggisberg, D. , and Koch, H. (1995). *Mitt. Gebeite Lebensm. Hyg*. 86: 14-28 - single lab data prvided to CCRVDF by Switzerland.	full recommendation
				kidney		10000	100			
				muscle		500	100			
				fat		500	100			
				milk		1500	100	60th JECFA	FAO Food & Nutrition Paper 41/15	
				liver	pig	500	100	43rd JECFA; data provided to CCRVDF	FAO Food & Nutrition Paper 41/7; Giggisberg, D. , and Koch, H. (1995). *Mitt. Gebeite Lebensm. Hyg*. 86: 14-28.	provisional recommendation
				kidney		10000	100			
				muscle		500	100			
				fat		500	100			
		Yes	LC	kidney		10000	100		For method provided to 13th CCRVDF, contact Animal Research Institute, Chemical Residue Laboratory, 665	provisional recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									Fairfield Road, Yeerongpilly QLD 4105, Australia.	
		Yes		eggs	chicken	500	450		See Report of 12th Meeting, CCRVDF.	provisional recommendation
Nicarbazin	N,N'-bis-(4-nitrophenyl) urea	Yes	LC	liver	chicken	200	100	50th JECFA; data provided to CCRVDF	FAO Food & Nutrition Paper 41/11; Data provided by Argentina to 16th CCRVDF	full recommendation
				kidney		200	100			
				muscle		200	100			
				fat/skin		200	100			
Oxfendazole (see febantel, etc.)										full recommendation
Oxytetracycline (see chlortetracycline, etc.)										As per chlortetracycline
Phoxim	Phoxim	Yes	LC	liver	pig	50	10	52nd JECFA	FAO Food & Nutrition Paper 41/12	full recommendation
				kidney		50	10			
				muscle		50	10			
				fat		400	10			
			GC	liver	sheep, goat	50	50			
				kidney		50	50			
				muscle		50	50			
				fat		400	50			
Pirlimycin	Pirlimycin	Yes	LC/MS	liver	cattle	1000	250	62nd JECFA	FAO Food & Nutrition Paper 41/16 - additional validation with current generation equipment	provisional recommendation
				kidney		400	50			
				muscle		100	50			
				fat		100	50			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									requested.	
				milk		100	50			
Procaine benzylpenicillin (see benzylpenicillin)	Benzylpenicillin	Yes	LC	liver	cattle, pig, chicken	50	5		See benzylpenicillin	As per benzylpenicillin
				kidney		50	5			
				muscle		50	5			
				fat		50	5			
Ractopamine	Ractopamine	Yes	LC	liver	cattle	40	5	62nd JECFA	FAO Food & Nutrition Paper 41/16	full recommendation
				kidney		90	5			
				muscle		10	5			
				fat		10	5			
				liver	pig	40	5			
				kidney		90	5			
				muscle		10	5			
				fat		10	5			
Sarafloxacin	Sarafloxacin	Yes	LC	liver	chicken	80	5	50th JECFA	FAO Food & Nutrition Paper 41/11	full recommendation
				kidney		80	5		NOTE: For regulatory method for poultry and fish muscle provided to CCRVDF contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France.	
				muscle		10	5			
				fat		20	5			
				liver	turkey	80	5			
				kidney		80	5			
				muscle		10	5			
				fat		20	5			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Spectinomycin	Spectinomycin	Yes	LC	liver	cattle	2000	100	50th JECFA	FAO Food & Nutrition Paper 41/11; see also Report of 12th Meeting, CCRVDF: method issued by German Federal Institute for Consumer Health Protection and Veterinary Medicine, applicable to spectinomycin residues in muscle, kidney, liver and fat of calves, pigs and chickens, and in egg.	full recommendation
				kidney		5000	100			
				muscle		500	100			
				fat		2000	100			
				milk		200	100			
				liver	pig	2000	100			
				kidney		5000	100			
				muscle		500	100			
				fat		2000	100			
				liver	sheep	2000	100			
				kidney		5000	100			
				muscle		500	100			
				fat		2000	100			
				liver	chicken	2000	100			
				kidney		5000	100			
				muscle		500	100			
				fat		2000	100			
				eggs		2000	250	42nd JECFA	FAO Food & Nutrition Paper 41/6; further method validation for analysis of tissues provided in FAO Food & Nutrition Paper 41/11.	

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Spiramycin	Sum of Spiramycin and Neospiramycin	Yes	LC	liver	cattle	600	62.5	data provided to CCRVDF; 43rd & 47th JECFA	FAO Food & Nutrition Papers 41/7 & 41/9; data (1 lab) provided to CCRVDF for LC; 47th JECFA reviewed microbiological growth inhibition and LC methods; NOTE: For regulatory method provided to CCRVDF for muscle tissue contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France.	full recommendation
				kidney		300	30			
				muscle		200	30			
				fat		300	47			
		Yes	microbial growth inhibition	milk		200	62		FAO Food & Nutrition Paper 41/7; LOQ listed is for the microbiological growth inhibition assay using ATCC 9341 as indicator organism.	provisional recommendation
		Yes	LC	liver	pig	600	300	47th JECFA	FAO Food & Nutrition Paper 41/9	full recommendation
				kidney		300	300			
				muscle		200	100			
				fat		300	115			
				liver	chicken	600	100	43rd JECFA	FAO Food & Nutrition Paper 41/7; method suitability confirmed by 47th JECFA, FAO Food & Nutrition Paper	
				kidney		800	200			
				muscle		200	50			

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
				fat		300	75		41/9.	
Streptomycin (see Dihydrostreptomycin and Streptomycin)									FAO Food & Nutrition Paper 41/14; see also Gerhardt, G.C., Salisbury, C.D.C., & MacNeil, J.D. (1994) *J. AOAC Int.* 77: 334-337; data provided to CCRVDF by Canada, 2nd laboratory verification of performance reported by UK.	full recommendation
Sulfadimidine	Sulfadimidine	Yes	TLC	liver	cattle	100	20	Data provided to CCRVDF by U.S. and Canada.	AOAC Official Method 983.31: Sulfonamide Residues in Animal Tissues. (1995). *AOAC Official Methods of Analysis, 16th edition.* AOAC International, Gaithersburg, MD. (method extension).	full recommendation
				kidney		100	20			
				muscle		100	20			
		Yes	LC	milk		25	10	Data provided to CCRVDF by U.S.	AOAC Official Method 992.21 : Sulfamethazine Residues in Raw Bovine Milk. (1996). *AOAC Official Methods of Analysis, 16th edition, Supplement March 1996.* AOAC International,	full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									Gaithersburg, MD.	
		Yes	TLC	liver	pig	100	20	Data provided to CCRVDF by U.S.	AOAC Official Method 983.31: Sulfonamide Residues in Animal Tissues. (1995). *AOAC Official Methods of Analysis, 16th edition.* AOAC International, Gaithersburg, MD.	full recommendation
				kidney		100	20	Data provided to CCRVDF by U.S. and Canada.	AOAC Official Method 983.31: Sulfonamide Residues in Animal Tissues. (1995). *AOAC Official Methods of Analysis, 16th edition.* AOAC International, Gaithersburg, MD. (method extension).	full recommendation
			TLC, LC	muscle		100	20	1. Data provided to CCRVDF by US. 2. Data provided to CCRVDF by Germany.	1. AOAC Official Method 983.31: Sulfonamide Residues in Animal Tissues. (1995). *AOAC Official Methods of Analysis, 16th edition.* AOAC International, Gaithersburg, MD. 2. Malisch, R., Bourgeois, B. and	full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									Lippold, R. (1992). *Deutsch. Lebensm. Rdsch.* 88: 205-216 .	
		Yes	TLC	liver	sheep	100	20	Data provided to CCRVDF by U.S. and Canada.	AOAC Official Method 983.31: Sulfonamide Residues in Animal Tissues. (1995). *AOAC Official Methods of Analysis, 16th edition.* AOAC International, Gaithersburg, MD. (method extension).	full recommendation
				kidney		100	20			
				muscle		100	20			
		Yes	TLC	liver	poultry	100	20	Data (turkey, duck) provided to CCRVDF by U.S. Extension to chicken: U.S. and Canada.	AOAC Official Method 983.31: Sulfonamide Residues in Animal Tissues. (1995). *AOAC Official Methods of Analysis, 16th edition.* AOAC International, Gaithersburg, MD.	full recommendation
				kidney		100	20			
				muscle		100	20			
Tetracycline (see chlortetracycline, oxytetracycline, tetracycline)	Parent drug, alone or in combination	Yes	LC						See Chlortetracycline, Oxytetracycline, Tetracycline (above).	as per chlortetracycline

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Thiabendazole	Sum of thiabendazole and 5-hydroxythiabendazole	Yes		liver	cattle	100		Info provided to 13th CCRVDF	NOTE: For regulatory method provided to CCRVDF by Australia, contact Amdel. 36-40 Halloran St., Lilyfield NSW 2040, Australia.	provisional recommendation
		Yes		milk		100		Info provided to 13th CCRVDF	NOTE: For regulatory method provided to CCRVDF contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France	
		Yes		liver	pig	100		Info provided to 13th CCRVDF	NOTE: For regulatory method provided to CCRVDF by Australia, contact Amdel. 36-40 Halloran St., Lilyfield NSW 2040, Australia.	provisional recommendation
		Yes		liver	sheep	100		Info provided to 13th CCRVDF	NOTE: For regulatory method provided to CCRVDF by Australia, contact Amdel. 36-40 Halloran St., Lilyfield NSW 2040, Australia.	provisional recommendation
Tilmicosin	Tilmicosin	Yes	LC	liver	cattle	1000	50	47th JECFA	FAO Food & Nutrition Paper 41/9	provisional recommendation
		Yes	LC	kidney		300	10	Data provided to CCRVDF	Chan, W., Gerhardt, G.C., &	full recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
				muscle		100	10	by Canada; 2nd laboratory data provided by UK.	Salisbury, C.D.C. 1994. *J. AOAC Int.* 77:331-333. NOTE: For alternate regulatory method for muscle tissue provided to CCRVDF contact AFSSA-LERMVD, Javene, BP090203-35302, Fougeres, France.	
		Yes	LC	fat		100	50	47th JECFA	FAO Food & Nutrition Paper 41/9	
				liver	pig	1500	20			
		Yes	LC	kidney		1000	10	Data provided to CCRVDF by Canada; 2nd laboratory data provided by UK.	Chan, W., Gerhardt, G.C., & Salisbury, C.D.C. 1994. *J. AOAC Int*. 77:331-333.	
				muscle		100	10			
		Yes	LC	fat		100	20	47th JECFA	FAO Food & Nutrition Paper 41/9	
				liver	sheep	1000	50			
		Yes	LC	kidney		300	10	Data provided to CCRVDF by Canada; 2nd laboratory data provided by UK.	Chan, W., Gerhardt, G.C., & Salisbury, C.D.C. 1994. *J. AOAC Int*. 77:331-333.	
				muscle		100	10			
		Yes	LC	fat		100	50	47th JECFA	FAO Food & Nutrition Paper 41/9	
			LC	milk		50	50	47th JECFA	FAO Food & Nutrition Paper 41/9: LOQ is usually at least 1/2	provisional recommendation

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
									the MRL - validation of method to 25 µg/kg recommended.	
Trenbolone acetate	β-Trenbolone (liver)	Yes	LC	liver	cattle	10		Data provided to 15th CCRVDF by Canada	MacNeil, J.D., Reid, J.A., Neiser, C.D. & Fesser, A.C.E. (2003). *J. AOAC Int*. 86: 916-924.	provisional recommendation
	α-Trenbolone (muscle)			muscle		2				
Trichlorfon (metrifonate)	Trichlorfon	Yes	GC/MS	liver	cattle	50	50	54th JECFA	FAO Food & Nutrition Paper 41/13; MRLs for tissue are based on LOQ of method - no residues were deteted in tissues in the depletion studies.	full recommendation
				kidney		50	50			
				muscle		50	50			
				fat		50	50			
				milk		50	25			
Triclabendazole	5-Chloro-6-(2',3'-dichlorophenoxy)-benzimidazole-2-one	Yes	LC	liver	cattle	300	20-50	Data provided to CCRVDF by Switzerland.	Marti, A.M., Mooser, A.E., and Koch, H. (1990). *J. Chromatogr*. 498: 145-157. Data provided to CCRVDF for performance of method for pig liver, kidney and muscle tissues.	provisional recommendation
				kidney		300	20-50			
				muscle		200	20-50			
	NOTE: For regulatory method for triclabendazole residues in cattle and sheep liver provided to CCRVDF by Australia, contact Amdel. 36-40 Halloran St., Lilyfield NSW 2040, Australia.									

Compound	Marker Residue	Method Recommended	Technique	Tissue	Species	MRL (µg/kg)	LCL or LOQ (µg/kg)	Verified By	Reference	Method Status
Zeranol	Zeranol	Yes	GC/MS	liver	cattle	10	0.5	Data provided to CCRVDF by U.S. and Canada.	Chemistry Laboratory Guidebook. United States Department of Agriculture, Food Safety and Inspection Service, Science Program, Washington, D.C. Results of multi-lab trial provided for review to CCRVDF.	full recommendation
				muscle		2	0.5			

Appendix XI

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

Name of the Compound	Question (s) to be answered	Data Availability	Proposed By	Comments
Dexamethasone	Request to recommend MRLs in cattle (tissues, milk); horses (tissues) and pigs (tissues).	Canada can provide method[1].	Canada	Previously evaluated by 50th JECFA, which established temporary MRLs. Minimal data needs (analytical method).
Tylosin	Request to establish ADI and recommend MRLs in poultry (tissues, eggs); pigs (tissues); cattle (tissues) and honey.	Additional data available by early 2008.	Germany	Previously evaluated by 38th JECFA.
Kanamycin	Request to establish ADI and recommend MRLs in cattle (tissues, milk); sheep (tissues, milk); poultry (tissues); pigs (tissues).	Some microbiological data from Korea, rest unknown[1].	Republic of Korea	Not previously evaluated by JECFA.
Avilamycin	Request to establish ADI and recommend MRLs in poultry (tissues), pigs (tissues) and rabbit (tissues).	Company has advised that data for poultry, pigs and rabbit will be available in 2008.	Brazil	Not previously evaluated by JECFA.
Bacitracin	Request to establish ADI and recommend MRL in poultry (tissues) and pigs (tissues).	Unknown[1].	Brazil	Previously evaluated by 12th JECFA in 1968.
Flavophospholipol	Request to establish ADI and recommend MRLs in poultry (tissues) and pigs (tissues).	Unknown[1].	Brazil	Not previously evaluated by JECFA.
Nitrofurans[2]	Request to establish ADI and recommend MRLs in cattle, pigs, poultry, fish and shrimp – all relevant tissues (tissues, eggs, milk) and honey.	Unknown[1].	France	Furazolidone and Nitrofurazone previously evaluated by 40th JECFA in 1993. Include nitrofurans in Annex III of the report from the Working Group to develop recommendations on veterinary drugs without ADI/MRLs.
Malachite Green	Request to establish ADI and recommend MRLs in fish (tissues).	Some literature data available[1].	Germany	Not previously evaluated by JECFA.
Tilmicosin	Request to recommend MRL in sheep (milk).	New data is available.	United States	Previously evaluated by 54th JECFA.
Xylazine	Request to establish ADI and recommend MRLs in cattle (tissues, milk) and deer (tissues).	New data is available.	Germany New Zealand	Previously evaluated by 47th JECFA but no ADI or MRLs were established.

1 The type of data and its date of availability to be confirmed to the JECFA Secretariat by July 2006.

2 All compounds with an intact 5-nitro group.