codex alimentarius commission

FOOD AND AGRICULTURE
ORGANIZATION
OF THE UNITED NATIONS

WORLD HEALTH
ORGANIZATION

JOINT OFFICE: Via delle Terme di Caracalla 00100 ROME Tel.: 57971 Telex: 625852-625853 FAO I Cables: Foodagri Rome Facsimile: (6) 57973152-5782610

ALINORM 93/31

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION
Twentieth Session
Geneva, Switzerland, 28 June - 7 July 1993

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

Washington, D.C., 22-25 October 1991

Note: This document incorporates Codex Circular Letter CL 1991/26-RVDF

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CX 4/60.2

CL 1991/26-RVDF
November 1991

TO: - Codex Contact Points
- Interested International Organizations
- Participants at the Sixth Session of the Codex Committee on Residues of Veterinary Drugs in Foods

FROM: Chief, Joint FAO/WHO Food Standards Programme, FAO, Via delle Terme di Caracalla, 00100 Rome, Italy

SUBJECT: Distribution of the Report of the Sixth Session of the Codex Committee on Residues of Veterinary Drugs in Foods (ALINORM 93/31)

The report of the Sixth Session of the Codex Committee on Residues of Veterinary Drugs in Foods is attached. It will be considered by the Twentieth Session of the Codex Alimentarius Commission, to be held in Geneva from 28 June - 7 July 1993.

PART A: MATTERS FOR ADOPTION BY THE COMMISSION

The following matters will be brought to the attention of the 20th Session of the Codex Alimentarius Commission for adoption:

1. Draft Maximum Residue Limits for Veterinary Drugs at Step 8; paras. 30, 32 and Appendix II, ALINORM 93/31.

2. Draft Glossary of Terms and Definitions at Step 8; paras. 61-63 and Appendix IX, ALINORM 93/31.

Governments wishing to propose amendments or to comment on the above draft Maximum Residue Limits or the Glossary of Terms and Definitions should do so in writing in conformity with the Guide to Consideration of Codex Standards at Step 8 (see Codex Alimentarius Procedural Manual, Seventh Edition) to the Chief, Joint FAO/WHO Food Standards Programme, FAO, Via delle Terme di Caracalla, 00100 Rome, Italy, not later than 31 May 1993.

3. Proposed Draft Maximum Residue Limits for Veterinary Drugs at Steps 5/8; paras, 34-35, 37-40 and Appendix IV, ALINORM 93/31

Governments wishing to propose amendments or to submit comments regarding the implications which the proposed draft Maximum Residue Limits or any provisions thereof may have for their economic interests should do so in writing in conformity with the Procedure for the Elaboration of Worldwide Codex Standards (at Steps 5 and/or 8) (see Codex Alimentarius Procedural Manual, Seventh Edition) to the Chief, Joint FAO/WHO Food Standards Programme, FAO, Via delle Terme di Caracalla, 00100 Rome, Italy, not later than 31 May 1993.

PART B: REQUEST FOR COMMENTS AND INFORMATION

1. Draft Code of Practice for Control of the Use of Veterinary Drugs: (paras. 54-56 and Appendix VII, ALINORM 93/31)

The Committee agreed to return the draft Code to Step 6 for additional government comments.

2. Draft Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods; (paras. 57-60 and Appendix VIII, ALINORM 93/31)

The Committee agreed to return the general introductory section of the Guidelines, along with those annexes already finalized by the *Ad Hoc* Working Group on Methods of Analysis and Sampling, to Step 6 for additional government comments.

3. Veterinary Drugs Not Assigned an Acceptable Daily Intake (ADI) or Maximum Residue Limit (MRL) by JECFA; (paras. 49-52 and Appendix VI, ALINORM 93/31)

The Committee agreed to request government comments concerning possible action to be taken for those veterinary drugs not assigned an ADI or MRL by JECFA (i.e., the "inactive list").

4. Evaluation of Older Veterinary Drugs (paras. 23, 49, 83, 90 and 92, ALINORM 93/31)

The Committee agreed to request comments for submission to the JECFA Secretariat concerning the means by which governments evaluate older veterinary drugs.

Governments and international organizations wishing to submit comments and information on the above matters are invited to do so not later than 15 May 1992 and as directed below:

For points B.1 to B.3 above:

Dr. Gerald B, Guest
Director, Center for Ve inary Medicine (HFV-1)
Food and Drug Administra .on
5600 Fishers Lane
Rockville, MD. 20857 (U.S.A.)
Telefax No. 301.295.8830
Telex No. 898488 PHS PKLN ROV

For point B.4 above:

Dr. J.L. Herrman
International Programme on Chemical Safety
Division of Environmental Health
World Health Organization
CH-1211 Geneva 27
Switzerland
Telefax No. 7910746
Telex No. 415416

In addition, please forward a copy of the comments to: Chief, Joint FAO/WHO Food Standards Programme, FAO, Via delle Terme di Caracalla, 00100 Rome, Italy.

SUMMARY AND CONCLUSIONS

The Sixth Session of the Codex Committee on Residues of Veterinary Drugs in Foods reached the following conclusions during its deliberations:

Matters for Consideration by the Commission

- Recommended the adoption of **draft MRLVDs for albendazole and trenbolone acetate** at Step 8 by the 20th Session of the Codex Alimentarius Commission, (paras. 30 and 32);

- Recommended the adoption of **proposed draft MRLVDs for closantel, (sheep tissue only), ivermectin, benzylpenicillin, oxytetracycline and carbadox** under accelerated elaboration procedures at Steps 5/8 by the 20th Session of the Codex Alimentarius Commission, (paras. 34-35, 38-40);

- Recommended the adoption of the **Draft Glossary of Terms and Definitions** at Step 8 by the 20th Session of the Codex Alimentarius Commission, (para. 63);

Other Matters of Interest to the Commission

- Agreed to retain a draft **MRLVD for sulfadimidine** (at Step 7) and **proposed draft MRLVDs for closantel (cattle only), levamisole, carazolol, spiramycin, febantel, fenbendazole and oxfendazole** at Step 4 for additional discussions at a future CCRVDF session, pending their re-examination by JECFA, (para. 31, 34, 36 and 53);

- Agreed to return the draft **Code of Practice for Control of the Use of Veterinary Drugs** to Step 6 for additional government comments, (para. 55);

- Agreed to return the draft **Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods** to Step 6 for additional government comments, (para. 59);

- Agreed to advance the **Proposed Draft Code of Practice for the Use of Veterinary Drugs in Aquaculture** as part of the Code of Hygienic Practice for Aquaculture under development by the CCFFP for government comments at Step 3, (para. 66);

- Agreed to request the Executive Committee to examine a proposal concerning the **process by which MRLVDs are adopted by the Commission**, (para. 16);

- Agreed to request government comments concerning possible action to be taken for those **veterinary drugs not assigned an ADI or MRL** by JECFA (i.e., the "inactive list"), (para. 52);

Other Matters of Interest to the Commission (cont'd)

- **Agreed to request government comments and the views of JECFA concerning the evaluation of "older drugs"**, (para. 92);

- Agreed to have the OIE present a progress report on its elaboration of a draft **Code of Practice for the Registration of Veterinary Drugs** to the next CCRVDF session, (para. 68);

- Agreed to have the United States present a progress report on the **Compendium of Veterinary Drugs** at the next CCRVDF session, (para. 71);

- Agreed to discontinue the **Survey of Intake Studies** and to forward the data to JECFA for its information and use, (para. 75);

- Agreed to endorse those methods recommended and the continuation of the ***Ad Hoc* Working Group on Methods of Analysis and Sampling** under the Chairmanship of the United States, (para. 82) and;

- Agreed to endorse those priorities recommended and the continuation of the ***Ad Hoc* Working Group on Priorities** under the Chairmanship of Australia, (para. 94).

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LIST OF APPENDICES

INTRODUCTION

1. The Codex Committee on Residues of Veterinary Drugs in Foods held its Sixth Session in Washington, D.C., at the kind invitation of the Government of the United States of America. The Session was chaired by Dr. Gerald B. Guest, Director, Center of Veterinary Medicine, United States Food and Drug Administration. It was attended by 34 member countries of the Commission and 9 international organizations.

2. The Session was preceded by meetings of the *Ad Hoc* Working Group on Methods of Analysis and Sampling under the Chairmanship of Dr. Richard Ellis (United States) and the *Ad Hoc* Working Group on Priorities under the Chairmanship of Dr. J. Owusu (Australia). The reports of the Working Groups were presented to the Plenary under Agenda Items 15 and 16 respectively.

3. A list of participants at the Session, including officers of the Secretariat, is attached to this report as Appendix 1.

OPENING OF THE SESSION (Agenda Item 1)

4. Dr. Alejandro Thiermann, U.S. Coordinator for Codex Alimentarius, addressed the Committee at the invitation of the Chairman. He referred to the continuing importance of the work of the Committee within the framework of the Codex Alimentarius Commission. He noted that in response to the challenge presented by the GATT Uruguay Round of trade negotiations the Commission would be responsible for bringing together consumers, industry and government regulators to develop internationally recognized standards and thereby contribute to fairness in trade and safety of the foods available to the consumer. Dr. Thiermann then introduced Dr. Stuart Nightingale, Associate Commissioner for Health Affairs of the United States Food and Drug Administration, who opened the Session.

5. Dr. Nightingale emphasized the increased significance and importance of Codex standards to assure international agreement on permitted levels of veterinary drug residues in foods. Dr. Nightingale highlighted the importance of basing standards on objective data and sound scientific criteria and principles. He reaffirmed continued support of the Government of the United States for the Joint FAO/WHO Food Standards Programme and other important related programmes. Dr. Nightingale suggested that trade agreements should adequately reflect consumer concerns regarding the safety of foods. He stated that there was a need to consider and respond to consumer concerns early in the evaluation and decision-making processes and to seek the cooperation of consumer groups to educate the public about scientific issues. Dr. Nightingale concluded his remarks by stating that the ultimate success of the Codex process will rest on cooperation between the government, industry, and consumers.

ADOPTION OF THE AGENDA (Agenda Item 2)

6. The Committee had before it the Provisional Agenda for the Session as contained in document CX/RVDF 91/1, and document CX/RVDF 91/1 - Add.1, which contained a supplementary list of an item proposed for inclusion in the Agenda under the provisions of Rule V.5 of the Rules of Procedure of the Codex Alimentarius Commission. The Committee adopted the Provisional Agenda and the Supplementary List as the Agenda for its present session.

APPOINTMENT OF RAPPORTEUR (Agenda Item 3)

7. The Committee appointed Dr. Dieter Arnold (Germany) to serve as Rapporteur for the Session.

MATTERS OF INTEREST ARISING FROM THE CODEX ALIMENTARIUS COMMISSION AND OTHER CODEX COMMITTEES (Agenda Item 4 (a))

8. The Committee had before it working paper CX/RVDF 91/2, which summarized matters of interest arising from activities of the Commission and other Codex

Committees. The Committee also had before it a paper prepared by the United States (CX/RVDF 91/2-Add.1) on "Implications for the Codex Committee on Residues of Veterinary Drugs in Foods of the Codex Alimentarius Commission Vote not to Adopt JECFA Recommendations for Growth Promoting Cattle Hormones at Step 8".

Matters of interest arising from the 19th Session of the Codex Alimentarius Commission and Other Codex Committees

9. The Committee decided to discuss those matters of interest arising from the Commission specific to points on its agenda under the relevant agenda item and therefore, limited its discussions to the following issues.

10. The Committee noted the opinion of the Commission in relation to the elaboration of Codex Advisory Texts and agreed that the procedure recommended by the Commission, namely that advisory texts should be subject to full and transparent elaboration procedures, was applicable to the advisory texts under current elaboration by the Committee (paras. 98-100, ALINORM 91/40).

11. In relation to the Commission's decision to hold the draft MRL for Chloramphenicol at Step 8 (paras. 163-164, ALINORM 91/40), the Committee was informed that subsequent action by the Commission would depend on the outcome of the 1993 JECFA evaluation. Should the present evaluation remain unchanged, it was foreseen that the Commission would consider the MRL at Step 8 without further discussion by the CCRVDF. On the other hand, should JECFA make an evaluation which differed from the present evaluation, the Commission would follow the established procedures whereby the CCRVDF would first consider the draft MRL at intermediate steps.

Codex Committee on Meat Hygiene

12. The Committee noted that the Codex Committee on Meat Hygiene, which had met in the preceding week (14-18 October 1991), had expressed interest in the incorporation of a residue monitoring programme as part of its work in the *ante-mortem* and *post-mortem* inspection and judgement of slaughter animals and meat. Residues as defined by the Committee included veterinary drug and pesticide residues and contaminants as defined in the Codex Alimentarius. The Secretariat reported that a paper would be prepared for the Codex Committee on Meat Hygiene outlining the work of the various activities of Codex Committees responsible for work in these areas so that it would be possible to integrate this work in the meat hygiene codes in a manner which did not involve unnecessary duplication of work.

Implications for the Codex Committee on Residues of Veterinary Drugs in Foods of the Codex Alimentarius Commission Vote not to Adopt JECFA Recommendations for Growth Promoting Cattle Hormones at Step 8

13. In introducing document CX/RVDF 91/2-Add.1, the Delegation of the United States stated that a number of questions had arisen from the decision of the 19th Session of the Commission not to adopt, by vote, the Draft MRLs for growth-promoting hormones at Step 8. Principal among these was the need to ensure that the work of the Codex Alimentarius Commission was based on sound scientific principles. The Delegation stated that the procedural process allowed for scientific discussion, but that procedural reform was needed to ensure that the final recommendations of the Commission should be basically science-oriented. The Delegation noted that although no Delegation at the Commission Session or in the CC/RVDF during the elaboration process had questioned the safety of draft MRLs, the Delegation expressed concern that the vote on the Draft MRLs for hormones was perceived as a judgement on the safety of the substances. The Delegation referred to the recommendation contained in the document that the Commission should examine the process by which draft standards recommended by the Codex Committee which were based on thorough scientific assessments by JECFA are evaluated.

14. Several delegations and the Observer from COMISA supported the basic principles highlighted in the U.S. paper. Other delegations reserved their opinion. There was general consensus that the CCRVDF was not the appropriate body for the examination of procedural matters affecting many aspects of the Commission's work. It was alternatively proposed that the questions raised by the United States might be considered in the first instance by the Codex Committee on General Principles or the Executive Committee. It was pointed out that the FAO/WHO Conference on Food Standards, Chemicals in Foods and Food Trade, held in March 1991 in Rome, had stressed the need for scientific principles to be used as the basis of Codex work, for appropriate considerations of risk assessment to be incorporated in this process, and for the role of JECFA to be reinforced.

15. The Secretariat informed the Committee that the FAO Legal Counsel had noted that the Statutes, Rules and Procedures of the Commission did not bind the Commission to science as the basis of the decision-making process. Other factors, in particular economic considerations, were explicitly mentioned in the Procedural Manual and were available to the CAC in its deliberations. Nevertheless, the cumulative experience of the Commission was that decisions in the past had followed the recommendations of expert committees. In this case, the decision of the Commission not to adopt the Draft MRLs at Step 8 should be seen as a decision based on other considerations and that the scientific integrity of the safety evaluations had not been questioned. The principle problem was not with the safety of the substances and their residues, but in the public perception of their safety. The Secretariat stated that it was clear that the governments represented at the Commission had acted in the light of their own national situations, and that the Commission decision clearly reflected this. The Secretariat further stated that it would be preferable to consider the Commission decision as an isolated incident and not as a precedent for future considerations.

16. The Committee, without taking any position on the paper, requested the Executive Committee to examine the United States recommendation contained in the paper to determine whether the matter should be further discussed by the Codex Committee on General Principles or by the Commission itself.

MATTERS OF INTEREST ARISING FROM INTERNATIONAL ORGANIZATIONS (Agenda Item 4 (b))

World Health Organization (WHO)

17. The Representative of the World Health Organization noted that the report of a WHO Consultation on Public Health Aspects of Seafood-Borne Zoonotic Diseases (WHO/CDS/VPH/90.86) was available. Section 6 of the report considered possible hazards due to drugs used in aquaculture. Some of the problems in assessing risks and controlling drugs used in aquaculture and control measures already in force in many countries were described. Several recommendations were made, including development of "maximum acceptable levels" (maximum residue limits for veterinary drugs), perhaps through the Codex system.

18. The WHO Representative announced the availability of a catalogue of reports issued by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and a complete index of substances, including veterinary drugs, that have been evaluated by JECFA. The catalogue was available at no charge from Distribution and Sales, WHO, 1211 Geneva 27, Switzerland.

Pan American Health Organization (PAHO)

19. The Observer from PAHO outlined activities of this organization related to the work of the Codex Committee on Residue of Veterinary Drugs in Foods. Several activities were carried out with the main objectives to develop policies, plans and strategies; resource mobilization; information distribution; training, technical advice; and support of projects and research activities concerning:

- an evaluation of PAHO regional programmes of technical cooperation in food protection during the years 1986-1990;
- the risks of transmission of cholera through foods in cooperation with FAO, FDA, CDC and the USAID;
- the epidemiological surveillance of foodborne diseases;
- street vended foods especially in cooperation with FAO;
- paralytic shellfish poisoning (red tide);
- collaboration in a FAO/PAHO workshop on mycotoxins held in Costa Rica in February 1991;
- the analysis of residues of anabolic agents in meat;
- technical cooperation with Mexico and with Caribbean countries, and;
- the development and utilization of computerized information systems.

20. In addition, the observer indicated that future activities would focus on the organization of national integrated programmes for food protection; strengthening of laboratory and inspection services; establishing epidemiological surveillance systems for foodborne diseases and promoting food protection by community participation.

European Economic Community (EEC)

21. The Observer from the European Communities reported on activities directed towards the preparation of the entry into force of Regulation (EEC) 2377/90 concerning the establishment of Community MRLs for active substances used in veterinary medicines. It was reported that after the entry into force, no new active substance for use in food-producing animals may be authorized unless a Maximum Residue Limit had been established by the Community. An ambitious target had been set that by January 1997 MRLs must be established for all active substances used in food-producing animals. After that date it will not be possible to use any substance in food-producing animals for which no MRL had been set. Detailed guidance on the preparation and presentation of the information required was prepared and a timetable for the submission of data in respect of the "older" substances to be considered under the regulation was established.

22. The observer reported on progress in relation to the evaluation of Bovine Somatotropins (BST). An opinion expressed by the Committee on Veterinary Medicinal Products indicated that residues of this product did not represent a risk to the health of the consumers of meat or milk obtained from treated animals, however, some Members States of the Community had outstanding questions regarding the safety of the product for the target animal in particular as regards the incidence of mastitis and the possibility of injection site reactions.

Consultation Mondiale de l'Industrie de la Santé Animale (COMISA)

23. The Observer from COMISA reported on developments within that organization to strengthen communication between the worldwide research-based animal health industry and the Joint FAO/WHO Expert Committee on Food Additives. The Representative recalled that at the March 1991 Food Standards Conference it had called for a streamlining of the Codex Step Procedure and had stressed the urgent need for the formulation of an "older drug" policy. The need for such a policy was accentuated by the continuing requirement to ensure that drugs essential to the maintenance of animal health and production in developing countries remained available. The observer stated that COMISA remained committed to the goal of global harmonization of veterinary drug residue standards based on sound scientific

principles which would thereby contribute to free trade and better consumer protection.

Office International des Epizooties (OIE)

24. The Observer of the OIE provided updated information on the programmes of the Office in the field of veterinary drugs, with special attention to training and information activities. The representative reported that the Second Workshop of Veterinary Drug Registration in Africa had been held in Dakar, Senegal in March 1991. This Workshop dealt with matters such as veterinary drug legislation and technical requirements for registration. The Office had also organized in March 1991 an international conference on anti-infective chemotherapy in aquaculture, with particular emphasis being paid to the growing use of such products and their implication in public health and the environment.

25. OIE further reasserted its concern for achieving the widest international cooperation while developing its programme. This cooperation had been put into effect for a long time with the CCRVDF and the International Technical Consultation on Veterinary Drug Registration. It was recently extended to WHO to elaborate a compendium of major veterinary drugs.

International Technical Consultation on Veterinary Drug Registration (ITCVDR)

26. The Delegation of Argentina announced that the 6th ITCVDR will be held in Buenos Aires from 22-26 June 1992. The Delegation gave a brief outline of the preliminary programme.

International Dairy Federation (IDF)

27. The Observer from the IDF informed the Committee on activities being undertaken in the Federation; expert groups on Residues and Contaminants in Milk and Milk Products (A4), Pesticides (E12), and Detection of Antibiotics (E47). He reported that a monograph on residues and contaminants in milk and milk products had been completed. A revised monograph on detection of inhibitors (antibiotics and sulfa drugs) and a new monograph on special methods (mainly confirmatory methods) had also been published, as well as a provisional standard on the determination of organo-phosphorus compounds in milk. These documents were available from the IDF Central Secretariat in Brussels. Also available were the results of an interlaboratory comparative trial on detection limits of Penicillin G and tetracycline under practical conditions. The trial indicated that commercially available test kits did not always respond correctly to substances present at levels close to the draft MRLs under consideration by the Committee.

AOAC International

28. The Representatives of the Association of Official Analytical Chemists noted that the organization had changed its name to AOAC International so as to reflect its international membership and activities. He reported that the Association had embarked on two new methods evaluation programmes which were separate and different from the full collaborative study process. These were the "peer verified programme" which would be of particular use for regulatory agencies and others where a full collaborative study may not be possible. The "Certified Test Kit" programme was designated to provide for a third-party review of test kit performance as claimed by the test-kit manufacturer.

CONSIDERATION OF DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS (MRLVDs) ARISING FROM THE 34TH JECFA SESSION (Agenda Item 5)

29. The Committee had before it the Draft Maximum Residue Limits for Veterinary Drugs contained in Appendix III of ALINORM 91/31A. It was noted that these MRLVDs had been adopted by the 19th Session of the Commission at Step 5 of the Elaboration Procedure (paras. 165-167, ALINORM 91/40). Comments had been requested at Step 6

on the Draft MRLVDs by means of Codex Circular Letter CL 1991/7-RVDF, and comments in response to the Circular Letter were available to the Committee in document CX/RVDF 91/3 (Spain) and Conference Room Document 2 (EEC).

Albendazole

30. The Delegation of the Netherlands, speaking on behalf of the Member States of the European Community present at the Session, expressed its reservation on the MRLVDs on the basis that there was evidence that Albendazole was a direct selective teratogen, but did not oppose the advancement of the MRLVDs to the next Step. The Committee agreed to advance the Draft MRLVDs to Step 8 for the consideration of the Commission (see Appendix II).

Sulfadimidine

31. The Committee noted that the ADI and the MRLVDs for this substance were both temporary and that the substance was scheduled to be re-evaluated by JECFA in 1993. It therefore decided not to advance the MRLVDs for sulfadimidine at the present time, and to hold them at Step 7 (see Appendix III). It recommended that should the JECFA re-evaluation of the substance result in the confirmation of the temporary ADI and MRLVDs, then the substance should automatically be forwarded to the Commission for adoption at Step 8.

Trenbolone Acetate

32. The Delegation of the Netherlands, speaking on behalf of the Member States of the European Community present at the Session, referred to the position of the Community expressed at previous Sessions of the Committee, namely that it was inappropriate for MRLs to be established for growth-promoting agents. The Committee noted the opinion of the statement made by the Delegation of the Netherlands and decided to advance the MRLVDs for Trenbolone Acetate to Step 8 for the consideration of the Commission (see Appendix II).

CONSIDERATION OF PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS (MRLVDs) ARISING FROM THE 36TH JECFA SESSION **(Agenda Item 6)**

33. The Committee had before it the Proposed Draft Maximum Residue Limits for Veterinary Drugs contained in Appendix II of ALINORM 91/31A. Comments had been requested on the Proposed Draft MRLVDs by means of Codex Circular Letter CL 1990/41-RVDF, and comments in response to the Circular Letter were available to the Committee in document CX/RVDF 91/4 (Czechoslovakia, New Zealand, United States) and Conference Room Document 2 (EEC).

Closantel

34. The Committee noted that the Proposed Draft MRLVDs for Closantel in cattle were temporary and that the substance would be re-evaluated in 1992 by JECFA. It agreed to retain the Proposed Draft MRLVDs for Closantel in cattle at Step 4, pending further advice from JECFA (see Appendix V); however, the MRLVD for Closantel in edible tissues of sheep was advanced to Step 5 of the Procedure. In view of the fact that the Proposed Draft MRLVD had been considered twice by the Committee, it recommended to the Commission that the MRLVD for edible tissues of sheep be considered also at Step 8 by the omission of Steps 6 and 7 under the accelerated elaboration procedures (see Appendix IV).

Ivermectin

35. It was agreed to identify the species to which the Proposed Draft MRLVDs applied; namely the species on which information had been received and evaluated by JECFA. In the case of Ivermectin, for both liver and fat, the species identified were cattle, sheep and swine. On this basis the Committee advanced the MRLVDs for Ivermectin to Step 5 of the Procedure and recommended that the MRLVDs

be adopted by the Commission at Step 8 by the omission of Steps 6 and 7 (see Appendix IV).

Levamisole

36. The Committee noted that the ADI and the MRLVDs for Levamisole were temporary and that the substance was scheduled for review by JECFA in 1994. It therefore agreed to hold the Proposed Draft MRLVDs at Step 4 of the Procedure pending further advice from JECFA (see Appendix V). The species identified in relation to the MRLVDs were:

All edible tissues -	cattle, sheep, swine
Milk -	cattle.

Benzylpenicillin

37. The Committee noted that the species to which the MRLVDs applied were:

Liver, kidney, muscle -	cattle, swine
Milk -	cattle.

38. The Committee advanced the MRLVDs for Benzylpenicillin to Step 5 of the Procedure and recommended that the MRLVDs be adopted by the Commission at Step 8 by the omission of Steps 6 and 7, (see Appendix IV).

Oxytetracycline

39. The Committee noted that the JECFA evaluation had referred to the following species: cattle, sheep, swine, chickens, turkeys and fish. The Delegations of Norway, Sweden and Finland expressed concern on the basis that the MRLVDs for oxytetracycline exceeded the Minimum Inhibitory Concentration (MIC), and therefore could give rise to selective pressures on the gut microflora which had food safety implications. The Delegation of Sweden also found it necessary that the assessment of a possible risk of residues of antimicrobial drugs should be based on a more precise definition of "effects on the intestinal flora". When such an effect is evaluated effects on food derived from treated animals should be separated from possible effects on the environment. The latter effects should primarily influence the guidelines for the use of the drug and not the MRL-value. Other delegations noted that Symposia were being organized in London and Washington to consider objective criteria for the assessment of potential microbiological risks. These Delegations were of the opinion that such considerations should be brought to the attention of JECFA and discussed on a scientific basis by the Expert Committee. The Committee noted the opinions expressed above and advanced the MRLVDs for Oxytetracycline to Step 5 of the Procedure and recommended that the MRLVDs be adopted by the Commission at Step 8 by the omission of Steps 6 and 7 (see Appendix IV).

Carbadox

40. The Delegation of the Netherlands, speaking on behalf of the Member States of the European Community present at the Session, noted that this substance was regulated within the Community under regulations different to those for used other veterinary drugs and that it was necessary to reserve the position of the Community countries in relation to possible acceptance of a Codex MRL for this substance. The Committee advanced the MRLVDs for Carbadox to Step 5 of the Procedure and recommended that the MRLVDs be adopted by the Commission at Step 8 by the omission of Steps 6 and 7 (see Appendix IV).

CONSIDERATION OF PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS (MRLVDS) ARISING FROM THE 38TH JECFA SESSION (Agenda Item 7)

41. The Committee had before it a draft report of the 38th meeting of the Joint FAO/WHO Expert Committee on Food Additives (unnumbered), which had been distributed approximately two months before the Session, a summary report of the 38th JECFA meeting (CX/RVDF 91/5), and subsequent government comments that had been received (CX/RVDF 91/5 - Add.1 and Conference Room Document 2). The FAO and WHO Joint Secretaries of JECFA summarized the results of the meeting.

42. One beta-adrenoceptor blocking agent (Carazolol), three anthelmintic agents (febantel, fenbendazole, and oxfendazole), three antimicrobial agents (spiramycin, sulfadimidine, and tylosin), and three tranquillizing agents (azaperone, chloropromazine, and propionylpromazine) were on the agenda. Temporary acceptable daily intakes (ADIs) were allocated to carazolol, febantel, fenbendazole, oxfendazole, and spiramycin; the temporary ADI for sulfadimidine was extended. Temporary maximum residue limits (MRLs) were estimated for carazolol (cattle and pigs) and spiramycin (cattle and pigs). Temporary group MRLs were estimated for febantel, fenbendazole, and oxfendazole (cattle, sheep, and pigs) and the temporary MRLs for sulfadimidine that had been estimated at the 34th meeting of JECFA were extended. The data were insufficient for establishing ADIs or MRLs for tylosin, azaperone, chlorpromazine, or propionylpromazine.

43. Residues of several of the veterinary drugs under consideration had the potential to be pharmacologically active, and the General Considerations section of the JECFA report devoted considerable space to this issue. The current position of JECFA was that without evidence of testing of carcogenicity, ADIs could not be allocated to veterinary drugs even when pharmacological effects were observed at much lower levels than the toxicological effects.

44. The 38th JECFA expressed concern about potentially high residues of veterinary drugs at injection sites in edible tissue of an animal. In cases where JECFA believed this to be a possible problem, the expert committee may recommend further restrictions on the use of a drug.

45. At earlier JECFA meetings devoted to the evaluation of veterinary drugs, there were inconsistencies in the naming of animal species and other parameters when recommending MRLs. The 38th JECFA therefore decided upon the following requirements in recommending MRLs for veterinary drugs:

- All animal species will be named individually.
- The target tissues (muscle, fat, liver or kidney) or food product (milk, eggs) will be identified.
- The term "edible tissues" will be used only when a given MRL applies to all edible tissues of a named species. (This does not include milk and eggs which are animal products).
- The marker residue used in setting the MRL will be identified. If no marker residue is named, the MRL is established on the basis of the parent drug.

46. It was noted that the report of the 38th Session of JECFA will be published in the WHO Technical Report Series (No. 815), the toxicological evaluations in the WHO Food Additives Series (No. 29), and the residues monographs in FAO Food and Nutrition Paper Series (No. 41/4).

47. The Delegation of the Netherlands, speaking on behalf of the Member States of the European Community present at the Session, noted that even though there were minor differences in the ADIs and MRLs for carazolol between JECFA and those of the Committee for Veterinary Medicinal Products (CVMP) of the EEC, the residue working

party of the CVMP had recommended that the Community should use the ADI and MRLs proposed by JECFA, in the interest of international harmonization. The toxicological evaluation of febantel, fenbendazole, and oxfendazole was undertaken by CVMP on a different basis than by JECFA, although the ADIs for oxfendazole were of the same order of magnitude. However, there were major differences in MRLs. Since it appeared that JECFA had additional residue data available, the residues working party of the CVMP would reconsider all the available residues data.

48. The Delegation also noted that the MRLs recommended by JECFA for spiramycin corresponded to those recommended by the Working Party on the Safety of Residues within the EEC, and that CVMP intended to review tylosin to determine whether MRLs can be established. In contrast to JECFA, CVMP had allocated an ADI to azaperone, based on a pharmacological end point. The Community shared the concerns of JECFA about the use of chlorpromazine and propionylpromazine in food-producing animals and was considering appropriate regulatory action.

49. The Observer from COMISA expressed regret that the 38th meeting of JECFA did not recommend any full ADIs or MRLs and noted that such an outcome did not help achieve the goals of Codex. The observer further noted that it is obvious that there was an urgent need for an "older drugs" policy within JECFA, and indicated that COMISA stands ready to assist in this effort.

50. Discussion centred on the policy that should be developed by CCRVDF for veterinary drugs for which JECFA is not able to establish ADIs or MRLs because of a lack of data. The initiative for bringing such drugs to JECFA for re-evaluation rests with industrial sponsors who perform the studies that are recommended, as JECFA does not establish a date by which data should be submitted.

51. The view was expressed that it was unsatisfactory to include these drugs in the Codex step system if data were not forthcoming within a reasonable period of time and that at the end of such a period positive action should be taken to recommend that they not be used. On the other hand, it was pointed out that the absence of data does not necessarily imply a public health problem. The need was expressed to develop a policy to deal with veterinary drugs that fall into this category.

52. It was agreed to place azaperone, chloropromazine, propionylpromazine, and tylosin on an inactive list (see Appendix VI). Comments will be solicited regarding action that should be taken with those drugs.

53. The Committee agreed to hold the draft MRLVDs for carazolol and spiramycin, and the group MRLVDs for febantel, fenbendazole, and oxfendazole at Step 4 (See Appendix V).

DRAFT CODE OF PRACTICE FOR CONTROL OF THE USE OF VETERINARY DRUGS (Agenda Item 8)

54. The Delegation of the United Kingdom presented the draft code as prepared at the last CCRVDF Session (Appendix V, ALINORM 91/31A) as well as written comments from Spain at Step 6 submitted in response to CL 1991/7-RVDF, as contained in CX/RVDF 91/6. The Committee also noted comments from France. The 19th Session of the Commission had adopted the Code at Step 5 (paras. 168-169, ALINORM 91/40). Several delegations offered comments and suggestions concerning various aspects of the Code.

Status of the Draft Code of Practice for Control of the Use of Veterinary Drugs

55. The Committee decided to return the Code for an additional round of comments at Step 6. It would be examined at Step 7 by the CCRVDF at its Seventh Session, with a view towards forwarding the Code to the 20th Session of the Commission for adoption at Step 8. It was also agreed that comments would be solicited from appropriate FAO Divisions through the Secretariat.

56. The proposed draft Code of Practice for Control of the Use of Veterinary Drugs is attached to this report as Appendix VII.

DRAFT GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAMME FOR CONTROL OF VETERINARY DRUG RESIDUES IN FOODS (Agenda Item 9)

57. The Committee noted that at its Fifth Session it had decided to forward the general introductory section of the guidelines (Appendix VI, ALINORM 91/31A) to the Commission for adoption, with the understanding that separate annexes under development on regulatory control would be included in the future. The guidelines were adopted by the 19th Session of the Commission at Step 5 under the above conditions (paras. 170-171, ALINORM 91/40), and additional government comments were solicited at Step 6 under CL 1991/7-RVDF.

58. The Delegation of the United States indicated that the general introductory section of the guidelines was revised based on government comments submitted by France, which were incorporated into the revised guidelines as contained in document CX/RVDF 91/7.

Status of the Draft Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drugs Residues in Foods

59. The Committee agreed to append the revised draft introduction to the guidelines, along with those annexes already finalized by the Working Group (Parts I, II and III of CX/RVDF 91/13) to the report for additional government comments at Step 6, with the understanding that additional annexes or cross-references could be added to the guidelines in the future. It was also agreed that the guidelines would be circulated to participants at the Codex Committee on Meat Hygiene for information and comment.

60. The guidelines, which are attached to this report as Appendix VIII, will be discussed at the Seventh CCRVDF Session at Step 7.

DRAFT GLOSSARY OF TERMS AND DEFINITIONS (Agenda Item 10)

61. The Delegation of Canada introduced document CX/RVDF 91/8, which contained government comments at Step 6 on the Draft Glossary of Terms and Definitions (Appendix IV, ALINORM 91/31A) which were submitted subsequent to the adoption of the Glossary at Step 5 by the Commission (paras. 172-173, ALINORM 91/40). Comments have been received from Brazil, France and Spain in response to Codex Circular Letter CL 1991/7-RVDF. The Delegation of Canada noted that many of the comments received related to questions of translation from English into other languages. Several comments had also been made on Definitions which had already been adopted as final texts by the Codex Alimentarius Commission or had been established by JECFA.

62. The Committee agreed that definitions and terms adopted by the Commission or in established use by JECFA or other Codex Committees would remain unchanged so as to prevent confusion. The other terms and definitions required additional attention to ensure equivalency of meaning between the three languages used, and the attention of the Secretariat was drawn to this matter.

Status of the Draft Glossary of Terms and Definitions

63. The Committee agreed to advance the Draft Glossary of Terms and Definitions to Step 8 of the Procedure for adoption by the Commission. It was noted, however, that the Glossary was primarily intended for internal use by the Committee, and that it would remain subject to amendment as required. The draft Glossary is attached to this report as Appendix IX.

PROPOSED DRAFT CODE OF PRACTICE FOR THE USE OF VETERINARY DRUGS IN AQUACULTURE (Agenda Item 11)

64. The Committee had before it a Proposed Draft Code of Practice for the Use of Veterinary Drugs in Aquaculture (CX/RVDF 91/9), as prepared by the Delegation of Canada with the assistance of the Delegations of Norway and the United Kingdom, following discussions at the last session of the Committee and subsequent to a request by the Codex Committee on Fish and Fishery Products for advice in this area (see paras. 14-17, ALINORM 91/31A).

65. In discussing the Proposed Draft Code, attention was drawn to the fact that it was based on the parallel code on Control of the Use of Veterinary Drugs (see paras. 54-56), which applied principally to land animals. Several sections therefore required amendment to make the code suitable for the special needs of fish production, particularly regarding withdrawal times and the need to consider environmental factors. It was agreed to incorporate these changes into the Code before transmitting it to the Codex Committee on Fish and Fishery Products.

Status of the Proposed Draft Code of Practice for the Use of Veterinary Drugs in Aquaculture

66. It was agreed to advance the Proposed Draft Code of Practice for the Use of Veterinary Drugs in Aquaculture as part of the Code of Hygienic Practice for Aquaculture under development by the Codex Committee on Fish and Fishery Products for government comments at Step 3[1]. The Committee noted that further development of the Code would be the responsibility of the Codex Committee on Fish and Fishery Products within the framework of the comprehensive Code of Hygienic Practice for Aquaculture.

PROGRESS REPORT BY OIE ON THE DRAFT CODE OF PRACTICE FOR THE REGISTRATION OF VETERINARY DRUGS (Agenda Item 12)

67. The Committee had before it document CX/RVDF 91/10, which was a progress report prepared by the Office Internationale des Epizooties (OIE) on the Draft Code of Practice for the Registration of Veterinary Drugs. The Representative of the OIE, in introducing the paper, noted that comments had been received since the Fourth and Fifth Sessions of the Committee from Australia, Germany, Norway, Senegal, Spain, United Kingdom, and COMISA. Additional oral comments were provided to the Representative of the OIE on sections of the Draft Code. All of these comments were caused by translation problems in the different languages. It was agreed to request the OIE to amend the Draft Code accordingly, while the views of the Animal Health Division of FAO would be requested.

68. The Committee noted that the Code would remain under development by the OIE, and agreed that a progress report on its development would be provided at the Committee's next session.

PROGRESS REPORT ON COMPENDIUM OF VETERINARY DRUGS (Agenda Item 13)

69. The Committee noted that the Delegation of the United States had previously agreed (paras. 77-79, ALINORM 91/31A) to continue elaboration of the Compendium and to present a progress report at the current session.

70. The Delegation of the United States reported that it had collected information on the laws and regulations used throughout the world for registration of veterinary products. The second edition of the "Compendium of Regulations and Authorities for Registered Veterinary Products" was made available to all delegates

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1/ *Government comments at Step 3 will be requested through the Codex Committee on Fish and Fishery Products under CL 1991/28-FFP (November 1991).*

at this Session. The Compendium contained information from 57 cooperating countries, including names and addresses of current registration authorities in those countries. The document was also available in electronic form.

71. The Committee thanked the United States for its efforts. The Committee encouraged the submission of additional data by member countries and FAO to the United States in order to update the Compendium and to continue the development of a data base of registered veterinary products from each of the countries. A progress report will be presented at the next session by the United States.

FINAL SUMMARY REPORT ON THE SURVEY ON INTAKE STUDIES (Agenda Item 14)

72. The Committee had before it the final summary and compilation of dietary intake data in Conference Room Document 5 (CX/RVDF 91/12), as prepared by the United States. The Delegation of the United States had agreed (para. 203, ALINORM 87/31) to carry out a survey of monitoring activities of member countries concerning residues of veterinary drugs in foods. A questionnaire was elaborated for the survey of information.

73. The Delegation of the United States noted that fourteen member countries and one international organization had submitted food consumption data from their national surveys. These data indicated that the JECFA estimates for consumption of edible animal products were conservative values and therefore very protective of human health.

74. The Delegation of the United States noted that it may undertake a national dietary intake study in the near future. The Delegation requested communication with other member countries who plan dietary intake studies for veterinary drug residues so that similar methods for collection of data could be used.

75. The Committee thanked the United States for its efforts in preparing the final summary report and noted that additional data may be added in the future. It was agreed that this information arising from the survey would be forwarded to JECFA for its information and use.

CONSIDERATION OF METHODS OF ANALYSIS AND SAMPLING BASED ON RESPONSES TO THE INFORMATION WORK SHEET AND OTHER DOCUMENTATION (Agenda Item 15)

76. The Committee noted that the principle working paper for this item, CX/RVDF 91/13, had been discussed under Agenda Item 9. The Committee had before it Conference Room Document 4, "Report to the Plenary Session of the Fifth Meeting of the *Ad Hoc* Working Group on Methods of Analysis and Sampling." The Chairman of the Working Group, Dr. Richard Ellis (USA), introduced the report and noted that a total of 43 delegates and observers attended from Argentina, Australia, Canada, Peoples Republic of China, Denmark, Finland, France, Germany, Ireland, Netherlands, Norway, Sweden, Switzerland, United Kingdom and U.S.A. Observers from COMISA, AOAC and the Secretariat from the Joint FAO/WHO Expert Committee on Food Additive also attended the meeting.

77. The Working Group Chairman noted that the Group had been provided and had reviewed a draft paper entitled "The Role and Suitability of Screening Tests for a Residue Control Programme." The paper was well received by the Group and in the ensuing discussion several points were made regarding veterinary drug screening procedures. These were:

- The method must be able to detect the drug at concentration levels below the MRL.
- Test kits must have at least semi quantitative capability with a relatively simple clean-up step.
- There is a need to evaluate the quantitative claims of some test kits.

- For low cost tests, it is more likely that less stringent performance characteristics would be required.

- Screening tests which are significantly more sensitive than the relevant confirmatory test should be avoided.

- Microbiological methods are not to be excluded as screening tests.

- Pooling of samples for greater economies in screening tests must be done judiciously.

- Screening tests provide support for regulatory control programmes.

- Sampling plans can be modified to improve the probability of finding violations and thereby enhance consumer confidence in residue control programmes.

78. The Working Group discussed and strongly endorsed a phased approach to the adoption of analytical methods, where "provisional" status would be assigned to a method which appears promising but lacks sufficient data to confirm validation, is not yet published, or specific reagents are not commercially available. Having provisional status methods would permit use of an interim analytical method for residue control purposes pending final validation. In this connection, the Working Group decided that provisional status of a method should include:

(a) reasons for the classification with an outline of future expectations to develop a validated method;

(b) a proposed upper time limit of three years for the expected data to be obtained.

79. Methods of analysis were discussed for albendazole, benzyl penicillin, carazolol, carbadox, chloramphenicol, closantel, fenbendazole, ivermectin, levamisole, oxfendazole, oxytetracycline, sulfadimidine, trenbolone and zeranol. References for those methods which the Working Group recommended to the Committee are listed in those Appendixes referencing draft maximum residue limits.

80. The Working Group noted that there was a question regarding the identity of the metabolite material analyzed as quinoxaline carboxylic acid (QCA) in the carbadox analysis. The Committee agreed that this should be brought to the attention of JECFA.

81. The Committee agreed to adopt the following Working Group recommendations:

1. That a category of "provisional" methods for determining compliance with Codex MRLVDs be established.

2. That three methods be adopted for chloramphenicol as being suitable for regulatory control. The previously recommended method for albendazole, carbadox, ivermectin and zeranol were reaffirmed.

3. That methods for benzyl penicillin, carbadox, three methods for chloramphenicol, oxytetracycline (milk only) and trenbolone be given provisional status.

4. That further validation data be obtained on other promising candidate methods for evaluation by the Working Group. Member governments and drug sponsors are encouraged to provide this data.

5. Recognizing the dependence of some evaluated methods on the availability of specific microbiological and immunochemical or other reagents, that drugs sponsors be encouraged to make available a

consistent supply of such proprietary reagents as well as residue marker compounds.

82. The Committee thanked the Working Group and its Chairman for the report and decided to endorse the continuation of the *Ad Hoc* Working Group on Methods of Analysis and Sampling under the Chairmanship of Dr. Richard Ellis (U.S.A.).

PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION (Agenda Item 16)

83. The Committee had before it CX/RVDF 91/14 and Conference Room Document 2, which contained comments and proposals for additions to the priority list of veterinary drugs requiring evaluation submitted in response to CL 1991/3-RVDF, Conference Room Document 3, the report of the *Ad Hoc* Working Group on Priorities and Conference Room Document 1, a paper on the Difficulties in Establishing Maximum Residue Limits for Older Veterinary Drugs. The Chairman of the Working Group, Dr. J. Owusu (Australia), introduced the report of the Working Group and its recommendations.

84. Comments had been received from Australia, Czechoslovakia, European Economic Community (EEC), Sweden, and the United States. The Delegations of Australia and the United States and the EEC were of the view that the current list of drugs awaiting review will provide a substantial workload for the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and therefore did not consider it appropriate to propose other compounds at this time.

85. The Delegation of Czechoslovakia had nominated the drug Nitrovin for inclusion on the priority list on the basis that it was listed in Annex II of the EEC directive 70/524. The EEC representative indicated that this listing had been withdrawn because of a lack of information on the chemical. Furthermore, no country or sponsor declared support for Nitrovin. The Committee therefore considered it inappropriate for inclusion in the Priority List.

86. The Committee noted that all of the drugs recommended at its fifth session for (Appendix VII, ALINORM 91/31A) priority attention by JECFA in 1992 had been placed on the agenda of the fortieth meeting of JECFA, except for rafoxanide.

87. Because of the large number of veterinary drugs on the list proposed for evaluation by JECFA in 1993 the present session prioritized them primarily on the basis of data availability. Those for which data availability was assured were kept on the 1993 list; others were placed on the 1994 list except for lindane and phenothiazine, which were placed into the category "substances not yet scheduled for evaluation". Lindane was removed from the priority list because the Committee was not aware of adequate supervised residue data from direct application to livestock that would permit the establishment of MRLVDs. It noted that the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) had established MRLs for egg, meat of cattle, pigs, sheep, milk, and poultry meat (fat). Trimethoprim was removed from the priority list because it is used almost exclusively in combination with sulfonamide, and sufficient specific information on trimethoprim may not be available.

88. It was recognized that there would be some advantages to grouping classes of substances together, such as the quinolones and aminoglycosides. However, it was not known whether data on oxolinic acid could be made available in time for consideration in 1993. It was noted that the JECFA Secretariat had the discretion to move a substance from 1994 to 1993 if there were valid reasons to do so. The WHO Joint Secretary of JECFA pointed out that the list for 1993 may be too extensive, and that one or more of the drugs on the list may have to be deferred to 1994.

89. The Committee agreed on the priority list as presented in Appendix X. This list includes those substances that were known to be scheduled for re-evaluation by JECFA at the time of the present session of CCRVDF.

90. In discussing the difficulties in establishing MRLs for older veterinary drugs (Conference Room Document 1), the Committee was informed that WHO had retained a consultant to develop criteria to be used by JECFA for the evaluation of these compounds. This initiative was taken in response to concern about the fact that ADIs or MRLs have not been able to be allocated by JECFA for several substances because of the fact that the data do not meet modern criteria. WHO, in cooperation with FAO, was currently gathering information that could be used to consider approaches to be taken for toxicologically evaluating older veterinary drugs and establishing MRLs. These approaches would be considered at the 40th meeting of JECFA.

91. The Delegation of the United States encouraged a re-examination of the appropriateness of microbiological endpoints for antibiotics as currently used in standard setting, and encouraged JECFA to consider reports of forthcoming symposia that will be held to consider this subject. The WHO Joint Secretary of JECFA assured the Delegation that reports of such symposia will be made available at future meetings of JECFA. However, the Delegation of France cautioned that, while useful, the results of these symposia were unlikely to resolve the issues regarding antimicrobial effects. The Delegation of Norway expressed the view that the issue of antibiotic resistance remained of real concern.

92. Various Delegations expressed the view that future sessions of CCRVDF should consider issues relating to the evaluation of older drugs. It was decided that a circular letter would be distributed to governments requesting information on ways that they deal with older veterinary drugs (to be sent to the JECFA Secretariat). The report of the fortieth meeting of JECFA will contain information on the development of criteria, which will be considered as a separate agenda item at the Seventh Session of CCRVDF.

93. The representative of COMISA noted that some confusion existed as to the weight given to each of the criteria used in selecting compounds for inclusion in the priority list. The Working Group agreed that COMISA would prepare and submit a paper on this topic for its consideration.

94. The Committee thanked the Working Group and its Chairman for its report and decided to endorse the continuation of the *Ad Hoc* Working Group on Priorities under the chairmanship of the Delegation of Australia. The Committee also agreed that a questionnaire regarding the nomination of veterinary drugs for priority evaluation should be circulated for comment.

OTHER BUSINESS AND FUTURE WORK (Agenda Item 17)

95. The Committee agreed that its discussions at its next session would include:

- Consideration of Maximum Residue Limits for Veterinary Drugs at Steps 4 and 7;
- Consideration of the Report of the 40th Session of JECFA;
- Consideration of the Draft Guidelines on the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods at Step 7;
- Consideration of the Draft Code of Practice for Control of the Use of Veterinary Drugs at Step 7;
- Consideration of government comments and the views of JECFA concerning the evaluation of "older drugs", and the treatment of drugs not assigned ADIs or MRLs by JECFA;
- Consideration of Methods of Analysis and Sampling for veterinary drug residues in foods;

- Consideration of the Priority List of veterinary drugs requiring evaluation; and

- Progress reports on the Draft Code of Practice for the Registration of Veterinary Drugs (OIE), and on the Compendium of Veterinary Drugs (USA).

DATE AND PLACE OF THE NEXT SESSION (Agenda Item 18)

96. The Committee was informed that its Seventh Session would be held from 20-23 October 1992 in Washington, D.C.. The Working Group meetings on Methods of Analysis and Sampling and on the Priority List would be held on Monday 19 October 1992.

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Summary Status of Work

Code/Guideline/Maximum Residue Limit	Step	For Action by:	Document Reference
Draft Maximum Residue Limits for Veterinary Drugs	8	20th CAC	ALINORM 93/31, Appendix II
Proposed Draft Maximum Residue Limits for Veterinary Drugs	5/8	20th CAC	ALINORM 93/31, Appendix IV
Draft Glossary of Terms and Definitions	8	20th CAC	ALINORM 93/31, Appendix IX
Draft Maximum Residue Limits for Veterinary Drugs	7	JECFA 7th CCRVDF	ALINORM 93/31, Appendix III
Proposed Draft Maximum Residue Limits for Veterinary Drugs	4	JECFA 7th CCRVDF	ALINORM 93/31, Appendix V
Draft Code of Practice for Control of the Use of Veterinary Drugs	6	Governments 7th CCRVDF	ALINORM 93/31, Appendix VII
Draft Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods	6	Governments 7th CCRVDF	ALINORM 93/31, Appendix VIII
Proposed Draft Code of Practice for the Use of Veterinary Drugs in Aquaculture	3	Governments 20th CCFFP	ALINORM 93/31, paras. 64-66; CL 1991/28-FFP
Process by which MRLVDs are adopted by the Commission	--	39th CCEXEC 10th CCGP 7th CCRVDF	ALINORM 93/31, paras. 13-16
Veterinary Drugs not assigned an ADI or MRL	--	Governments 7th CCRVDF	ALINORM 93/31, Appendix VI
Evaluation of Older Veterinary Drugs	--	Governments JECFA 7th CCRVDF	ALINORM 93/31, paras. 23, 49, 83, 90, 92
Methods of Analysis and Sampling	--	Governments 7th CCRVDF	ALINORM 93/31, paras. 76-82

Summary Status of Work (Cont'd)

Code/Guideline/Maximum Residue Limit	Step	For Action by:	Document Reference
Priority List of Veterinary Drugs Requiring Evaluation	--	Governments 7th CCRVDF	ALINORM 93/31, Appendix X
Progress Report on Compendium of Veterinary Drugs	--	United States 7th CCRVDF	ALINORM 93/31, paras. 69-71
Progress Report on the Code of Practice for the Registration of Veterinary Drugs	--	OIE 7th CCRVDF	ALINORM 93/31, paras. 67-68

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ALINORM 93/31
Appendix II

DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS
(Advanced to Step 8 of the Procedure)

Note: Section 5 - Reference to JECFA Reports - contains references to the reports of meetings of the Joint FAO/WHO Expert Committee on Food Additives, as published in the WHO Technical Report Series (TRS). Relevant toxicological monographs are published in the WHO Food Additives Series (FAS) and residue monographs of the substances concerned are published in the FAO Food and Nutrition Paper (FNP) Series.

1.	Substance: Albendazole	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-50 µg/kg body weight
3.1	(a) Commodity	(a) Muscle, fat and milk
	(b) MRL	(b) 100 µg/kg
	(c) Definition of residues on which MRL was set	(c) 2-aminosulfone metabolite
3.2	(a) Commodity	(a) Liver and kidney
	(b) MRL	(b) 5000 µg/kg
	(c) Definition of residues on which MRL was set	(c) 2-aminosulfone metabolite
4.	Reference to recommended methods of analysis	FDA, Center for Veterinary Medicine, NADA 110-048. Ellis, R.L., USDA, Food Safety and Inspection Service, Analytical Chemistry Laboratory Guidebook, Method 5.034.
5.	References to JECFA reports	WHO TRS 788 (1989) WHO FAS 25 (1990) FAO FNP 41/2 (1990)
6.	References to previous Codex publications	Appendix III, ALINORM 91/31 Appendix III, ALINORM 91/31A
1.	Substance: Trenbolone acetate	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-0.02 µg/kg body weight
3.1	(a) Commodity	(a) Muscle (cattle)
	(b) MRL	(b) 2 µg/kg
	(c) Definition of residue on which MRL was set	(c) Beta-trenbolone
3.2	(a) Commodity	(a) Liver (cattle)
	(b) MRL	(b) 10 µg/kg
	(c) Definition of residues on which MRL was set	(c) Alpha-trenbolone

4.	Reference to recommend method of analysis	Hendrics, D.M., *et al*, J. Animal Science, (1983), 57, 247-end, (provisional). Scheid, J.P., Roussel UCLAF, Division Agro-Vétérinaire, (provisional)
5.	References to JECFA reports	WHO TRS 683 (1982) WHO TRS 696 (1983) WHO TRS 763 (1988) WHO TRS 788 (1989) FAO FNP 41 (1988) FAO FNP 41/2 (1990) WHO FAS 23 (1988) WHO FAS 25 (1990)
6.	References to previous Codex publications	Appendix VI, ALINORM 89/31 Appendix V, ALINORM 89/31A Appendix III, ALINORM 91/31 Appendix III, ALINORM 91/31A

ALINORM 93/31
Appendix III

DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS
(Retained at Step 7 of the Procedure)

Note: Section 5 - Reference to JECFA Reports - contains references to the reports of meetings of the Joint FAO/WHO Expert Committee on Food Additives, as published in the WHO Technical Report Series (TRS). Relevant toxicological monographs are published in the WHO Food Additives Series (FAS) and residue monographs of the substances concerned are published in the FAO Food and Nutrition Paper (FNP) Series.

1.	Substance: Sulfadimidine	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-4 µg/kg body weight (Temporary)
3.1	(a) Commodity	(a) Meat, liver, kidney and fat
	(b) MRL	(b) 300 µg/kg (temporary)
	(c) Definition of Residue on which MRL was set	(c) Total residue
3.2	(a) Commodity	(a) Meat, liver, kidney and fat
	(b) MRL	(b) 100 µg/kg (temporary)
	(c) Definition of residue on which MRL was set	(c) sulfadimidine
3.3	(a) Commodity	(a) Milk (cattle)
	(b) MRL	(b) 50 µg/l (temporary)
	(c) Definition of residue on which MRL was set	(c) Total residue
3.4	(a) Commodity	(a) Milk (cattle)
	(b) MRL	(b) 25 µg/l (temporary)
	(c) Definition of residue on which MRL was set	(c) sulfadimidine
4.	References to recommended method(s) of analysis	(a) Journal of the Association of Official Analytical Chemists Vol. 66 (1983) pp. 881, 884 (b) Journal of Agriculture and Food Chemistry May-June 1981, pp. 621-624
5.	Reference to JECFA Reports	WHO TRS 788 (1989) WHO TRS 815 (1991) WHO FAS 25 (1990) FAO FNP 41/2 (1990)
6.	References to previous Codex Publications	Appendix III, ALINORM 91/31 Appendix III, ALINORM 91/31A

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Appendix IV

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS
(Advanced to Steps 5 and 8 of the Procedure)

NOTE: Section 5 - Reference to JECFA Reports - contains references to the reports of meetings of the Joint FAO/WHO Expert Committee on Food Additives, as published in the WHO Technical Report Series (TRS). Relevant toxicological monographs are published in the WHO Food Additives Series (FAS) and residue monographs of the substances concerned are published in the FAO Food and Nutrition Paper (FNP) Series.

1.	Substance: Closantel	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-30 µg/kg body weight
3.1	(a) Commodity	(a) edible tissues (sheep)
	(b) MRL	(b) 1500 µg/kg
	(c) Definition of residues on which MRL was set	(c) closantel
4.	Reference to recommended methods of analysis	(To be elaborated)
5.	References to JECFA reports	WHO TRS 799 (1990) WHO TRS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A
1.	Substance: Ivermectin	
2.	Acceptable Daily intake (ADI) as established by JECFA	0-0.2 µg/kg body weight
3.1	(a) Commodity	(a) Liver (cattle, sheep, pigs)
	(b) MRL	(b) 15 µg/kg
	(c) Definition of residues	(c) 22,23 dihydroavermectin B1a (H2B1a)
3.2	(a) Commodity	(a) Fat (cattle, sheep, pigs)
	(b) MRL	(b) 20 µg/kg
	(c) Definition of residues on which MRL was set	(c) 22,23 dihydroavermectin B1a (H2B1a)
4.	Reference to recommended methods of analysis	USDA/FSIS Chemistry Laboratory Guidebook Method No. 5.035
5.	References to JECFA reports	WHO TRS 799 (1990) WHO FAS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A

1.	Substance: Benzylpenicillin	
2.	Acceptable Daily Intake (ADI) as established by JECFA	30 µg/person/day (Daily intake of the parent drug should be kept below this level)
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) Liver, kidney and muscle (cattle and pigs) (b) 50 µg/kg (c) Benzylpenicillin
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) Milk (cattle) (b) 4 µg/kg (c) Benzylpenicillin
4.	Reference to recommended methods of analysis	(To be elaborated)
5.	References fo JECFA reports	WHO TRS 430 (1969) FAO NMRS 45 (1969) WHO TRS 799 (1990) WHO FAS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A
1.	Substance: Oxytetracycline	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-3 µg/kg body weight
3.1	(a) Commodity (b) MRL (c) Definition of Residue on which MRL was set	(a) muscle (cattle, sheep, pigs, chickens, turkeys, fish) (b) 100 µg/kg (c) Oxytetracycline
3.2	(a) Commodity (b) MRL (c) Definition of residue on which MRL was set	(a) Liver (cattle, sheep, pigs, chickens, turkeys) (b) 300 µg/kg (c) Oxytetracycline
3.3	(a) Commodity (b) MRL (c) Definition of residue on which MRL was set	(a) Kidney (cattle, sheep, pigs) (b) 600 µg/kg (c) Oxytetracycline
3.4	(a) Commodity (b) MRL (c) Definition of residue on which MRL was set	(a) Fat (cattle, sheep, pigs, chickens, turkeys) (b) 10 µg/kg (c) Oxytetracycline
3.5	(a) Commodity (b) MRL (c) Definition of residue on which MRL was set	(a) Milk (cattle) (b) 100 µg/l (c) Oxytetracycline

3.6	(a) Commodity (b) MRL (c) Definition of residue on which MRL was set	(a) Eggs (chickens) (b) 200 µg/kg (c) Oxytetracycline
4.	Reference to recommended methods of analysis	McWeeney, D.J. *et al*, Food Science Laboratory, MAFF (to be published), (Provisional)
5.	References to JECFA reports	WHO TRS 430 (1969) FAO NMRS 45 (1969) WHO TRS 799 (1990) WHO FAS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A
1.	Substance: Carbadox	
2.	Acceptable Daily Intake (ADI) as established by JECFA	Limited acceptance of residues
3.1	(a) Commodity (b) MRL (c) Definition of Residue on which MRL was set	(a) liver (pigs) (b) 30 µg/kg (c) Quinoxaline-2-carboxylic acid
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle (pigs) (b) 5 µg/kg (c) Quinoxaline-2-carboxylic acid
4.	Reference to recommended methods of analysis	USDA/FSIS Chemistry Labratory Guidebook Method No. 5.014. Lynch, M. and Bartolucci, R.O., J. Association of Analytical Chemists, (1982), 65, 66-70, (Provisional)
5.	Reference to JECFA reports	WHO TRS 799 (1990) WHO FAS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A

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Appendix V

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS
(Retained at Step 4 of the Procedure)

NOTE: Section 5 - Reference to JECFA Reports - contains references to the reports of meetings of the Joint FAO/WHO Expert Committee on Food Additives, as published in the WHO Technical Report Series (TRS). Relevant toxicological monographs are published in the WHO Food Additives Series (FAS) and residue monographs of the substances concerned are published in the FAO Food and Nutrition Paper (FNP) Series.

1.	Substance: Closantel	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-30 µg/kg body weight
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle (cattle) (b) 500 µg/kg (Temporary) (c) closantel
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) kidney (cattle) (b) 2000 µg/kg (Temporary) (c) closantel
3.3	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) liver (cattle) (b) 1000 µg/kg (Temporary) (c) closantel
4.	Reference to recommended methods of analysis	(To be elaborated)
5.	References to JECFA reports	WHO TRS 799 (1990) WHO TRS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A
1.	Substance: Levamisole	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-3 µg/kg body weight (Temporary)
3.1	(a) Commodity (b) MRL (c) Definition of Residue on which MRL was set	(a) muscle, liver, kidney, fat (cattle, sheep, pigs) milk (cattle) (b) 10 µg/kg (Temporary) (c) Levamisole
4.	Reference to recommended methods of analysis	(To be elaborated)

5.	Reference to JECFA reports	WHO TRS 799 (1990) WHO FAS 27 (1991) FAO FNP 41/3 (1991)
6.	References to previous Codex publications	Appendix II, ALINORM 91/31A
1.	Substance: Carazolol	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-0.1 µg/kg body weight (Temporary)
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle and fat (cattle and pigs) (b) 5 µg/kg (Temporary) (c) Carazolol
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) liver and kidney (cattle and pigs) (b) 30 µg/kg (Temporary) (c) Carazolol
4.	Reference to recommended methods of analysis	(To be elaborated)
5.	Reference to JECFA reports	WHO TRS 815 (1991) WHO FAS 29 (1991) FAO FNP 41/4 (1991)
6.	Reference to previous Codex publications	None
1.	Substance: Spiramycin	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-5 µg/kg body weight (Temporary)
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle (cattle and pigs) (b) 50 µg/kg (Temporary) (c) Spiramycin
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) liver (cattle and pigs) (b) 300 µg/kg (Temporary) (c) Spiramycin
3.3	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) kidney (cattle and pigs) (b) 200 µg/kg (Temporary) (c) Spiramycin
3.4	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) milk (cattle) (b) 150 µg/l (Temporary) (c) Spiramycin
4.	Reference to recommended methods of analysis	(To be elaborated)

5.	References to JECFA reports	WHO TRS 815 (1991) WHO FAS 29 (1991) FAO FNP 41/4 (1991)
6.	References to previous Codex publications	None
1.	Substance: Febantel	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-10 µg/kg body weight (Temporary)
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle, fat and kidney (cattle, sheep and pigs) (b) 100 µg/kg (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) liver (cattle, sheep and pigs) (b) 500 µg/kg (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
3.3	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) milk (cattle) (b) 100 µg/l (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
4.	References to recommended methods of analysis	(To be elaborated)
5.	References to JECFA reports	WHO TRS 815 (1991) WHO FAS 29 (1991) FAO FNP 41/4 (1991)
6.	References to previous Codex publications	None
1.	Substance: Fenbendazole	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-25 µg/kg body weight (Temporary)
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle, fat and kidney (cattle, sheep and pigs) (b) 100 µg/kg (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) liver (cattle, sheep and pigs) (b) 500 µg/kg (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
3.3	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) milk (cattle) (b) 100 µg/l (Temporary) (group MRL)[1] (c) Oxfendazole sulfone

4.	References to recommended methods of analysis	(To be elaborated)
5.	References to JECFA reports	WHO TRS 815 (1991) WHO FAS 29 (1991) FAO FNP 41/4 (1991)
6.	References to previous Codex publications	None

1.	Substance: Oxfendazole	
2.	Acceptable Daily Intake (ADI) as established by JECFA	0-4 µg/kg body weight (Temporary)
3.1	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) muscle, fat and kidney (cattle, sheep and pigs) (b) 100 µg/kg (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
3.2	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) liver (cattle, sheep and pigs) (b) 500 µg/kg (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
3.3	(a) Commodity (b) MRL (c) Definition of residues on which MRL was set	(a) milk (cattle) (b) 100 µg/l (Temporary) (group MRL)[1] (c) Oxfendazole sulfone
4.	References to recommended methods of analysis	(To be elaborated)
5.	References to JECFA reports	WHO TRS 815 (1991) WHO FAS 29 (1991) FAO FNP 41/4 (1991)
6.	References to previous Codex publications	None

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1 *Group MRL for febantel, fenbendazole, and oxfendazole individually or in combination. The MRL value is the sum of the residues of fendbendazole, oxfendazole, and oxfendazole sulfone, calculated as oxfendazole sulfone.*

LIST OF VETERINARY DRUGS EVALUATED BY JECFA ON WHICH NO ACTION HAS BEEN TAKEN BY THE COMMITTEE

Note: The current list indicates those substances evaluated by JECFA for which no maximum residue level could be recommended by the Expert Committee. The most usual reason for not establishing an MRL was the inadequacy of data provided to JECFA for evaluation. However, it is essential to consult the Expert Committee report for a full understanding of the status of the substance concerned.

Substance	JECFA Reference
Dimetridazole	34th Session, TRS 788 (1989)
Ipronidazole	34th Session, TRS 788 (1989)
Metronidazole	34th Session, TRS 788 (1989)
Ronidazole	34th Session, TRS 788 (1989)
Sulfathiazole	34th Session, TRS 788 (1989)
Diminazene	34th Session, TRS 788 (1989)
Isometamidium	34th Session, TRS 788 (1989)
Olaquindox	36th Session, TRS 799 (1990)
Tylosin	38th Session, TRS 815 (1991)
Azaperone	38th Session, TRS 815 (1991)
Chlorpromazine	38th Session, TRS 815 (1991)
Propionylpromazine	38th Session, TRS 815 (1991)

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Appendix VII

DRAFT CODE OF PRACTICE FOR CONTROL OF THE USE OF VETERINARY DRUGS AT STEP 6

Introduction

1. This Code sets out guidelines on the prescription, application, distribution, and control of drugs used for treating animals, preserving animal health or improving animal production. The Code is intended to apply to all States which are members of the organizations under whose auspices the project is being developed and to contribute towards the protection of public health.

2. Good practice in the use of veterinary drugs (GPVD), as defined by the CCRVDF, is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions. The maximum residue limit for veterinary drugs (MRLVD) may be reduced to be consistent with good practice in the use of veterinary drugs. The MRLVD is based on the type and amount of residue considered to be without toxicological hazard for human health while taking into account other relevant public health risks as well as food technological aspects.

3. Veterinary products (including premixes for manufacture of medicated feeding stuffs) used in food producing animals should be administered (or incorporated into feed) in compliance with the relevant product information approved by national authorities and/or in accordance with a prescription and/or instruction issued by a qualified veterinarian.

Registration and Distribution - General Requirements

4. All medicinal products (i.e., all veterinary therapeutic products) and medicinal premixes for inclusion in animal feeds should comply with the OIE Code of Practice for the Registration of Veterinary Drugs and be registered with the national authority. Products should only be distributed through veterinarians, registered wholesalers, pharmacists or other retail outlets permitted by national laws and regulations. Records of products taken into and leaving the premises should be maintained. Storage and transport conditions must conform to the specifications on the label, in particular those concerning temperature, humidity, light, etc.

Responsibility of the Veterinarian and of Others Authorized to Handle or Administer Medicines - General Provisions

5. Whenever veterinary drugs are handled or administered it is important to recognize that potentially hazardous effects may occur in animals or in human operators. When the administration of a medicine is not under direct veterinary supervision, it is therefore essential that, after the diagnosis, clear instructions should be provided on dose and methods of use, taking account of the competence of the user performing the work and ensuring that the correct calculation of, and the importance of adhering to, withdrawal periods is fully understood. It is similarly important to ensure that the farm facilities and management systems employed enable the withdrawal periods to be observed.

6. In determining treatments, it is necessary to ensure that an accurate diagnosis is obtained and be guided by the principles of maximum effectiveness combined with minimum risk. Specific treatments should be presented using as few products as possible and avoiding the use of

combination products, unless pharmacological advantages have been demonstrated.

7. Veterinarians should keep in mind that uncontrolled and unlimited use of medicinal products may lead to the accumulation of undesirable residues in the animals treated and in the environment, and that the continuous use of anticoccidial, antibacterial or anthelmintic products may favour the development of resistance. It is the responsibility of the veterinarian or other authorized persons to draw up programmes of preventive medicine for the farmer and to stress the importance of sound management and good husbandry procedures in order to reduce the likelihood of animal diseases. Every effort should be made to use only those drugs known to be effective in treating the specific disease.

8. The veterinarian should stress the need for diseased animals to be segregated from healthy animals and treated individually where possible.

9. Beyond his responsibility for advice on measures that will reduce the incidence of disease and for controlling it when it arises, the veterinarian is also responsible for taking the welfare of livestock fully into account.

Information of Veterinary Drugs

10. Product information considered essential by the national authority to ensure the safe and effective use of veterinary medicinal products must be made available in the form of labelling and nationally approved data sheets or leaflets. Information on dosage schedules should be complemented by instructions on dose-related recommended withdrawal periods, interactions, contra-indications and any other constraints on the use of the product including any precautions regarded as necessary.

Amounts to be Supplied

11. Medicines should not be supplied in excess of immediate requirements as this may lead to incorrect use or to deterioration of the products.

Preparation of Medicines

12. The preparation of medicines and medicated feeds should be undertaken by suitably trained personnel, using appropriate techniques and equipment.

Administration of Medicines

13. Special attention should be paid to the prescription and to using the correct dosage, site and route of administration. Note should be taken of all warning statements, interactions and contra-indications for use (in particular any incompatibility with other medicinal products). It is important not to use the product once the expiry date has passed.

14. In disease circumstances where no authorized product exists or certain indications or target species are not provided for in the product literature, the veterinarian can on his own responsibility or with advice from the manufacturer have recourse to other licensed products or off label use. Administration of products in this manner, however, may have unpredictable side effects and give rise to unacceptable residue levels. Veterinarians should therefore only embark on such uses, especially in food-producing animals, after the most careful consideration of the needs of the disease situation. Under these circumstances, a significantly extended withdrawal time should be assigned for drug withdrawal prior to marketing milk, meat or eggs. The veterinarian is responsible for providing written instructions on the use and withdrawal times for all medicines used off label. Off label use by persons other than veterinarians must not be

permitted except when such use is conducted or permitted under the supervision or prescription of the veterinarian.

15. To avoid the presence of unacceptable residues in meat or other by-products of animal origin it is essential that the livestock owner adheres to the withdrawal period laid down for each product and dose regime or to a suitably lengthy withdrawal period where none is specified. Full instructions should be given as to how this period is to be observed, including the use of on site residue detection methods where applicable and on the disposal of any animals slaughtered during treatment or before the end of the withdrawal period. If animals are sold before the end of the withdrawal period, the buyer must be informed.

Record Keeping Requirements

16. The veterinarian and/or the livestock owner or other authorized persons should keep a record of the products used, including the quantity, the date of administration, and the identity of animals on which the medicines were used. Each record should be kept for at least two years, and presented when required by the competent authorities.

Withdrawal of Veterinary Drugs

17. Where the veterinarian or other authorized person suspects that unexpected adverse reactions involving illness, abnormal clinical signs, or death in animals, or any harmful effects in persons administering veterinary medicines have been associated with a veterinary product they should be reported to the appropriate national authority. Regular feed-back or information to veterinarians and manufacturers on suspected adverse reactions should be encouraged.

Storage of Veterinary Drugs

18. Veterinary products should be correctly stored in accordance with label instructions. It should be kept in mind that storage temperatures are critical for some medicines, while exposure to light or to moisture can damage others. Prescription medicines should be separated from non-prescription medicines.

19. All veterinary products should be stored in secure premises and kept under lock and key where practicable and out of reach of children and animals.

Disposal of Veterinary Drugs

20. Veterinary drugs remaining after treatment has been completed must be disposed of safely. Partially used containers should not be retained for future use. Unused drugs beyond their expiry date may however be returned to the vendor if there is an agreement to that effect. Where administration of medicines is not under direct veterinary supervision, users should be advised about correct disposal measures, e.g., to reduce potential contamination of the environment.

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Appendix VIII

DRAFT GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAMME FOR CONTROL OF VETERINARY DRUGS RESIDUES IN FOODS
(At Step 6)

Governments need regulatory control programmes to ensure their citizens of a safe and wholesome food supply. Specifications of a residue control programme are determined by the importance of the various health risks that could be incurred by consumers of products derived from animal food products.

One type of risk may occur if meat is handled and consumed from animals excessively contaminated with microorganisms or toxins that could effect the health of consumers. This type of health risk can be minimized by establishing meat inspection programmes that emphasize appropriate and provide specific procedures on how to recognize the signs of disease in food producing animals.

Another kind of risk can occur if food animals have been raised using veterinary drugs or pesticides in an appropriate manner. The improper use of such chemicals can result in unsafe residues of these substances in food derived from the treated animals. The safety of the human food requires a full scientific evaluation of the relative hazard as well as quantity of a drug residue remaining in the tissues of treated livestock and poultry when used according to good veterinary practices, and a systematic set of procedures that will ensure effective control of such residues in human food.

In addition to the health protection benefits in having an effective residue control programme, a country with such a programme has the capability to participate in the community of food trading nations with greater confidence. This is because an effective residue control programme can also serve as the foundation for certifying the safety of the country's exported food products, as well as provide assurance of safety of such products imported into the country.

When establishing a programme for control of residues in foods, it is important to distinguish between the notion of "unbiased statistical sampling", where the samples are obtained from animals that are presented for inspection, and the notion of "biased or directed sampling", where samples are obtained from suspect food products. The purpose of unbiased statistical sampling is to determine the frequency of occurrence of contaminated products among those presented for inspection.

Samples are taken at random from food considered safe, and it is not necessary to retain these food products while waiting for the results of analytical testing. The sampling plan is determined beforehand, using statistical rules to ensure that the results are representative of the overall quality of the product(s) under consideration. The results may be used to certify the exported food products are in compliance with Codex MRLVDs. Conversely, directed sampling focuses on food products suspected of having residue concentrations that exceed the maximum residue limits. The food products are detained while waiting for results of laboratory testing, and are not released for human consumption should test results be unfavourable. The number of samples to be taken during the year for directed sampling may not, by definition, be predetermined. The results of directed sampling do not have statistical representativeness.

In establishing an effective residue control programme, a country should first establish a comprehensive system for determining the safety of veterinary drugs. This may be accomplished, for example, through an organization with suitable technical expertise and administrative authority. Veterinary drugs may be approved taking into consideration several relevant criteria, among which will be the safety evaluation of the veterinary drug for animals and for human food

consumption. The scientific evaluation of the safety of veterinary drugs is a long and rigorous task, that, perhaps, may not be necessary to perform in each country, especially in developing countries. Evaluation could be performed by the interested country, using the technical expertise of international organizations such as the FAO/WHO Joint Expert Committee on Food Additives (for veterinary drugs) for Codex, or the technical evaluation results in other countries having an acceptable, technically qualified safety assessment organizations.

To establish an effective programme for the control of residues of veterinary drugs in food, a country should include but not necessarily be limited to the following items:

1. Establishing the regulatory authority responsibility for implementing inspection programmes and laboratory analyses.

2. Elaborating an integrated inspection programme, including a residue control programme for the inspection of foods. The organization in charge of implementing this inspection programme should be granted the authority to take all the steps necessary to control products when residues exceed the maximum residue limits established for a food commodity.

3. Compiling a register of veterinary drugs and/or pure chemical; substances used in the country, including the products manufactured in the country and those products that are imported into the country.

4. Elaborating regulations concerning the distribution of veterinary drugs as a whole, providing for procedures for the authorized sale, manufacture, distribution and use of such products.

5. Elaborating procedures for determining the safety and efficacy of veterinary drugs in animals and residues in food from use of such veterinary drugs. This should include describing procedures for determining maximum residue limits for veterinary drugs in food and procedures for analysis of test samples intended to verify compliance with those limits.

6. Establishing procedures for sampling food products of animal origin, indicating the specific drug residues of greatest health concern, the number of samples to be taken for unbiased statistical sampling, and the nature of the tissue and quantity of sample to be taken. Procedures for sampling for residue control in a country may be required for certain substances for purposes other than the enforcement of MRLVDs. These analyses, for example, come within the scope of exploratory surveys for determining residues in foods where unapproved substances may be used in food producing animals or poultry. This type of data is essential to provide a residue control programme the flexibility necessary to be adapted to national needs.

7. Selecting the methods of analysis to be used. As an initial step, a residue control programme should include screening methods. The use of these methods should not require investment in complex laboratory instrumentation nor in costly reagents or personnel training, and should provide analysis of samples in a cost effective manner. Screening methods may be briefly defined as a qualitative or semi-quantitative method of analysis that detects the presence of a substance at a concentration that is equal to or lower than the maximum residue limits has been exceeded. Additional testing measures should be required, as determined by the objectives set forth in a country's residue control programme, to verify or confirm the results of screening methods.

8. Implementing a quality assurance programme to assure the highest quality results for methods of analysis. Such a programme will assure regulatory control authorities that the methods used will give reliable results that

are compatible with the MRLVD or within the limits established by national regulations.

9. Developing an educational programme(s) for producers and veterinarians providing instruction in the proper use of veterinary drugs, and encouraging the use of preventive measure to reduce the occurrence of residues in food animals and poultry.

For those countries that do not have the necessary technical capabilities for determining maximum residue limits, the FAO/WHO Joint Expert Committee on Food Additives (for veterinary drugs) may constitute a useful resource for obtaining these data.

10. Specific details concerning the establishment of a regulatory programme for control of veterinary drug residues in foods, as based on the above general principles, are attached to these guidelines as follows:

PART 1: Sampling for the Control of Residues of Veterinary Drugs in Foods

PART 2: General Considerations on Analytical Methods for Residue Control

PART 3: Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods

ALINORM 93/31
Appendix VIII
Part I

SAMPLING FOR THE CONTROL OF RESIDUES OF VETERINARY DRUGS IN FOOD

I. INTRODUCTION

1. Basis for the Sampling Principle

Based upon provisions in the 7th Edition, Codex Alimentarius Commission Procedural Manual, recommended sampling procedures for food additives, pesticide residues and residues of veterinary drugs in food have been exempted from the general sampling procedures of food commodities developed by the Codex Committee of Methods of Analysis and Sampling - Normal Practice. That committee's work is concerned mainly with sampling procedures for the visible and measurable qualities and attributes of various commodities and foods; sampling to determine whether standards of identity and composition have been met and to measure traditional attributes of quality, such as dust and moisture content in grain. The Codex Committees that are responsible for establishing permitted levels of regulated added substances - food additives, pesticides, veterinary drugs in food, have been given authority to prepare their own recommendations for methods of analysis and sampling. In this regard, the Codex Committee on Residues of Veterinary Drugs in Food established an ad hoc working group on methods of analysis and sampling at its first meeting.

2. General Principles

Sampling for analytical testing is only one element of a country's residue control program and, by itself, cannot accomplish the entire objective of protecting public health. Sampling is a tool used as part of the system for developing information to determine if a supply of foodstuffs meets public health requirements, in this case, that the concentration of veterinary drug residues are within specified limits.

Sampling has varying purposes and statistical parameters. This guideline discusses the various objectives which sampling may address and provides technical guidance to be applied for sampling products within the terms of reference of this Codex Committee. By using Codex standards, including agreed upon sampling methods, member countries can comply with Article III of the General Agreement on Tariffs and Trade.

In sampling for residues of an added, regulated substance such as a veterinary drug, it is important to sample as near as possible to where animals raised for food are cared for and slaughtered in herds or flocks. The most meaningful sampling for tissue residues will occur in conjunction with slaughter. For other food products within the scope of this Committee, such as honey, the most meaningful sampling for residues will occur at the time of collection, prior to commingling of samples from different producers.

Sampling at an abattoir in conjunction with slaughter of a herd or flock or with preliminary slaughter of a small number of test animals or birds, may involve testing samples drawn from live animals or birds. In these situations, analyses performed on tissues drawn from test animals or body fluids from live animals may provide test results for an inspector before a herd or flock is presented for slaughter or shipment. Analyses associated with pre-slaughter must be designed to prevent subsequent administration of drugs. In a like manner, for processed foods such as might be obtained from fish or honey, any sampling and testing must be designed to prevent subsequent administration of drugs. When body fluids are used for residue testing, care must be taken to have established tissue-fluid

relationships between the analytic results in these fluids and results in tissues where the MRLVD's are established.

Shortly after slaughter or after appropriately harvesting the principle food products, these products may be commingled to an extent that it destroys the possibility of drawing a representative sample. Samples for fresh meat or poultry or fresh chilled meat or poultry may be drawn from different days' production, for example. Processed products such as sausage or minced fish may be made with meat tissues from different days' or even different establishments' production. Although under some circumstances lots for sampling have been defined as products from the same consignor or packer, sample homogeneity can best be guaranteed when it is taken in conjunction with slaughter or primary collection point.

II. OBJECTIVES OF SAMPLING

A. Primary Point of Origin Sampling

1. Non-biased sampling

Non-biased sampling is designed to provide profile information on the occurrence of residues in specified food producing populations on an annual, national basis. For residue testing, the focus is on gathering information on the incidence of residue violations; therefore, only compounds with established safe limits such as MRLVD's are usually considered for residue testing programs. Compounds selected for statistically designed non-biased sampling are usually based on risk profiles (considering toxicity of residues and use) and the availability of laboratory methods suitable for regulatory control purposes. Information is obtained through a statistically based selection of random samples from animals presented for inspection. Limited or geographical area sampling may be conducted where a localized potential drug residue problem appears. The information obtained from this type of sampling should be reviewed periodically to assess residue control programs and to allocate resources according to specific needs.

In addition to profile information, residue data provides a basis for further regulatory action. In particular, the results can be used to identify producers marketing animals, or other food commodity within the terms of reference of this Committee, with violative concentrations of residues. When these producers subsequently bring animals, fish or honey for inspection, they will be subjected to more directed and specific sampling and testing until compliance with MRLVD's is demonstrated. Other auxiliary uses of the data are to indicate prevalence and concentrations of residue violations, to evaluate residue trends, and to identify residue problem areas within the industry where educational or other corrective efforts may be needed. Thus, non-biased sampling gathers information and assists in deterring practices that lead to residue violations.

As a general practice, samples collected by inspectors are sent for residue analysis to a laboratory designated by national authorities. Now, however, advances in analytical technology provide inspection authorities an opportunity for performing residue screening tests on commodities at an abattoir or similar facility. In these situations, inspectors may send tissue samples to a laboratory designated by national authorities for more definitive analyses when results obtained from the screening test suggest a positive residue finding.

In some cases and situations where samples are sent directly to a designated laboratory for residue testing, the laboratory results may not be available until after the product has moved into consumer markets and become untraceable. Because of this pragmatic limitation, some animals, fish or honey containing violative residues may inevitably pass into consumer markets, regardless of the regulatory control efforts to limit this occurrence as much as possible. The consequences to human health, however, are minimal as long as the frequency of violative residues is low. This is because MRLVD's represent the maximum residue concentration determined to be safe for daily consumption within the limits of the acceptable

daily intake (ADI) over a lifetime. As a result of employing safety factors for determining an ADI, and subsequently the MRLVD, the occasional consumption of products with slightly higher residue concentrations than the MRLVD is unlikely to result in adverse health effects.

Non-biased sampling should have a statistically specified reliability. This may be expressed in reference to a confidence level and an incidence rate. For example, sampling may be designed to detect, with 95% certainty, an incidence occurring in 1% of healthy animals submitted for inspection. When a confidence level and incidence rate is established, the number of samples necessary to achieve the desired objective can be determined from Table 1.

TABLE 1

TABLE 1. Number of samples required to detect at least one violation with predefined probabilities (i.e., 90, 95, and 99 percent) in a population having a known violation incidence.

Violation incidence (%) in a population	Minimum number of samples required to detect a violation 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
.5	460	598	919
.1	2302	2995	4603

2. Directed sampling

Directed sampling is designed to investigate and control the movement of potentially adulterated products. The sampling is often purposely biased and is directed at particular carcasses, products or producers in response to information from statistically based sampling (or other regulatory control agency data), or from inspector observations during ante-mortem or post-mortem inspection indicating that violative residues may be present. In-plant or on site residue testing procedures may be performed by the inspector, or samples may be submitted for analysis to a laboratory designated by national authorities. Depending upon the weight of evidence for testing in support of directed sampling, product may be retained until test results indicate the appropriate regulatory disposition. Laboratory analysis of directed residue test samples should be completed as rapidly as possible and take precedence over routine, statistically based samples. In directed sampling situations, herds of animals, flocks of birds, lots of fish or honey, should be considered unacceptable until it can be demonstrated that they are in compliance with Codex MRLVD's or national regulations in the country of origin for the specific commodity.

The probability of failing to detect a residue violation and accepting the lot depends upon the directed sampling programs' sample size and prevalence of the residue violation frequency. Table 2 shows the probability of failing to detect a residue violation using different sample sizes from an "infinite" population with a specified proportion of violations. For example, selecting 5 samples from a large lot in which 10 percent of the units contain violative residues would, on the average, fail to detect a residue violation in 59.0 percent of such lots (i.e.,

59.0 percent of the lots would be accepted). Assuming the same conditions as the previous example, but using a sample size of 50, would result in only 0.5 percent of such lots being accepted.

Risk and cost factors should be considered in determining the sample sizes used in a directed sampling programme. Also, because of possible gains in the probability of detecting unacceptable herds of animals, flocks of birds, lots of fish or honey due to residue violations, the feasibility of selecting separate samples from separate lots instead of from a single lot should be considered.

TABLE 2: PROBABILITY OF ACCEPTANCE (%)

	number of animals in sample tested									
prevalence	5	10	25	50	75	100	200	250	500	1000
1%	0.951	0.904	0.778	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	0.000			
6%	0.734	0.539	0.213	0.045	0.010	0.002	0.000			
7%	0.696	0.484	0.163	0.027	0.004	0.001	0.000			
8%	0.659	0.434	0.124	0.015	0.002	0.002	0.000			
9%	0.624	0.389	0.095	0.009	0.001	0.000				
10%	0.590	0.349	0.072	0.005	0.000					
12%	0.528	0.279	0.041	0.002	0.000					
14%	0.470	0.221	0.023	0.001	0.000					
16%	0.418	0.175	0.013	0.000						
18%	0.371	0.137	0.007	0.000						
20%	0.328	0.107	0.004	0.000						
24%	0.254	0.064	0.001	0.000						
28%	0.193	0.037	0.000							
32%	0.145	0.021	0.000							
36%	0.107	0.012	0.000							
40%	0.078	0.006	0.000							
50%	0.031	0.001	0.000							
60%	0.010	0.000								

B. Secondary Point of Sampling

1. Port of Entry Sampling

Port of entry testing of products derived from food producing animals, poultry, or fish, and honey, imported by member countries of Codex Alimentarius is a means of verifying the effectiveness of the exporting country's residue control program. The purpose of port of entry sampling and testing is not to replace an exporting country's residue control programmes.

Results of residue testing that indicate imported product is in compliance with Codex MRLVD's should be permitted to move into commerce. When test results indicate that imported product contains violative residues, subsequent shipments of the same product group from that establishment or company should be retained at the port of entry until laboratory results indicating compliance with MRLVD's are known by regulatory control authorities. Consideration should be given to placing

all subsequent shipments of similar products from the country of origin on an increased testing schedule until a record of compliance with Codex MRLVD's is reestablished.

Compounds selected for residue testing at port of entry should take into account the compounds approved for use in the exporting country, as well as those included in the domestic residue control program of the importing and exporting country. Guidance for collecting samples for port of entry testing is summarized in Annex A, Appendix A, Annex B, Appendix B and Annex C.

ANNEX A

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN MEAT AND POULTRY PRODUCTS

1. Objective

To provide instructions for sampling a lot of meat or poultry products to determine compliance with Codex maximum residue limits (MRLVD) for veterinary drugs.

2. Definitions

2.1 Lot

An identifiable quantity of food delivered for slaughter or 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

A quantity of food 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

A quantity of tissue taken from a single animal or 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 animal or location can be combined for the primary sample (such as poultry organs).

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The primary sample or a representative portion of the primary sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

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 Fat
No. 032 Mammalian Edible Offal

Type 07 Poultry Products

No. 036 Poultry Meats
No. 037 Poultry Fats
No. 038 Poultry, Edible Offal

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

Type 16 - Secondary Products

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**

For purposes of control, the maximum residue limit (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 none of the laboratory samples contains a residue greater than the MRLVD.

5. **Employment of Authorized Sampling Officials**

Samples must be collected by officials authorized for this purpose.

6. **Sampling Procedures**

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to take

During collection and processing, contamination or other changes in the samples which would alter the residue or affect the analytical determination must be prevented.

6.3 Collection of a Primary Sample

Detailed instructions for collection of a primary sample of various products are provided in Appendix A. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Appendix A. The following are general instructions.

a. Each primary sample should be taken from a single animal 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. Canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. The primary sample should contain a representative portion of juices surrounding the product. Each sample should then be frozen as described in paragraph 6.5.

d. Frozen product should not be thawed before sampling.

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

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If a residue violation is suspected because of its origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport, by signs of toxicosis observed during ante- or post-mortem inspection, or by other relevant information available to the 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.

6.41 Sampling Suspect Lots

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.

6.42 Sampling Non-Suspect Lots

A statistically-based, non-biased sampling program is recommended for non-suspect lots. Any of the following types of sampling can be used.

a. Stratified Random Sampling

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 program. A useful alternative sampling design is stratified random sampling which separates population elements into non-overlapping groups, called strata. Then 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 natural strata because of 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

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 too predictable, 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

In biased or estimated worst case sampling, the investigator should use their judgment and experience regarding the population, lot, or sampling frame to decide which samples to select. As a non-random technique, no inferences should be made about the population sampled based on data collected. The population group anticipated to be at greatest risk may be identified.

Exporting countries should conduct a comprehensive residue testing program 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 MRLVD's should be sampled as suspect lots.

6.5 Preparation of the Bulk Sample

The bulk sample is prepared by combining and thoroughly mixing the primary samples.

6.6 Preparation of the Final Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from it by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some National legislation may require the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Samples

a. Each sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged 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°C, immediately after collection, and packed in a suitable container that retards thawing. If possible, the shipping container should be placed in a freezer for 24 hours prior to packing and shipping the frozen sample.

7. Records

Each primary sample 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

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

APPENDIX A

MEAT AND POULTRY PRODUCTS

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
I. Group 030 (Maxmmalian 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.	0.5 kg
B. Small carcass (e.g., rabbit)	Collect hind quarter or whole carcass from one or more animals.	0.5 kg 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.	0.5 kg
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.	0.5 kg after removal of bone
D. Bulk frozen parts	Collect a frozen cross-section from selected container, or take muscle from one large part.	0.5 kg
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.	0.5 kg after removal of bone
Ia. Group 030 (Mammalian Meats where MRL is found in carcass fat)		
A. Animals sampled at slaughter	See instructions under II. Group 031.	
B. Other meat parts	Collect 0.5 kg 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

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
II. Group 031 (Mammalian fat)		
A. Large animals sampled at slaughter, usually weighing at least 10 kg	Collect kidney, abdominal, or subcutaneous fat from one animal.	0.5 kg
B. Small animals sampled at slaughter[1]	Collect abdominal and subcutaneous fat from one or more animals.	0.5 kg
C. Bulk fat tissue	Collect equal size portions from 3 locations in container.	0.5 kg
III. Group 032 (Mammalian Edible Offal)		
A. Liver	Collect whole liver(s) or portion sufficient to meet laboratory sample size requirements.	0.4 - 0.5 kg
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.	0.25 - 0.5 kg
C. Heart	Collect whole heart or ventricle portion sufficient to meet laboratory sample size requirement.	0.4 - 0.5 kg
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.	0.5 kg

[1] When adhering fat is insufficient to provide a suitable sample, the sole commodity within bone, is analyzed and the MRL will apply to the sole commodity (ALINORM 87/24, Appendix IV, paragraph 6).

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
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.	0.5 kg 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.	0.5 kg after removal of skin and bone
C. Whole carcasses of very small birds typically weighing less than 0.5 kg (e.g., quail, pigeon)	Collect at least 6 whole carcasses.	0.25 - 0.5 kg of muscle tissue
D. Fresh/chilled or frozen parts		
1. Wholesale packaged a. Large parts	Collect an interior unit from a selected container.	0.5 kg after removal of skin and bone
b. Small parts	Collect sufficient parts from a selected layer in the container.	
2. Retail packaged	Collect a number of units from selected container to meet laboratory sample size requirement.	0.5 kg 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 0.5 kg of fat or sufficient product to yield 50-100 g of fat. (Normally, 1.5-2.0 kg is required.)	0.5 kg of fat or enough tissue to yield 50-100 g of fat

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
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.	0.5 kg
VI. Group 038 (Poultry Edible Offal)		
A. Liver	Collect 6 whole livers or a sufficient number to meet laboratory sample requirement.	0.25 - 0.5 kg
B. Other fresh/chilled or frozen edible offal product	Collect appropriate parts from 6 birds. If bulk frozen, take a cross-section from container.	0.25 - 0.5 kg
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.	0.5 kg
B. Group 080 (Dried Meat Products)	Collect a number of packaged units in a selected container sufficient to meet laboratory sample size requirements.	0.5 kg, 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[2] (Manufactured, single ingredient product of animal origin)		

[2] For unit size less than 1 kg, apply the sampling described in CAC/PR-1984.

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
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.	0.5 kg 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.	0.5 kg 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[3] (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.	0.5 kg

[3] For unit size less than 1 kg, apply sampling as described in CAC/PR-1984.

ANNEX B

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN FISH, MILK, AND EGG PRODUCTS

1. Objective

To provide instructions for sampling a lot of eggs, milk, or aquatic animal products, to determine compliance with Codex maximum residue limits (MRLVD) for veterinary drugs.

2. Definitions

2.1 Lot

An identifiable quantity of food delivered for slaughter or 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

A quantity of food as described on a particular contractor's shipping document. Lots in a consignment may have different origins or be delivered at different times.

2.3 Primary Sample

A quantity of food taken from a single animal or from one place in the lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than location in the lot can be combined for the primary sample.

2.4 Bulk Sample

The combined total of all the primary samples taken from the same lot.

2.5 Final Sample

The bulk sample or a representative portion of the bulk sample to be used for control purposes.

2.6 Laboratory Sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. Commodities to which the Guideline Applies

3.1 Selected Class B: Primary Food Commodities of Animal Origin

Type 06 Mammalian Products
No. 033 Milks

Type 07 Poultry Products
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. 033, 039, 040, 041, 043, 045, 048, and 049

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

For purposes of control, the maximum residue limit (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 none of the laboratory samples contains a residue greater than the MRLVD.

5. Employment of Authorized Sampling Officials

Samples must be collected by officials authorized for this purpose.

6. Sampling Procedures

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to take

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 laboratory sample not representative of the bulk or final sample.

6.3 Collection of a Primary Sample

Detailed instructions for collection of a primary sample of various products are provided in Appendix B. Quantities to collect are dependent on the analytical method requirements. Minimum quantity requirements are included in Appendix B. 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. Canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the primary laboratory sample. Each primary sample should contain a representative portion of juices surrounding the product. Each sample should then be frozen as described in paragraph 6.5.

c. Frozen product should not be thawed before sampling.

6.4 The Number of Primary Samples to Collect from a Lot

The number of primary samples collected will vary depending on the status of the lot. If a residue violation is suspected because of its origin from a source with a past history of residue violations of the MRLVD, by evidence of contamination during transport or by other relevant information to the 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.

6.41 Sampling Suspect Lots

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.

6.42 Sampling Non-Suspect Lots

A statistically-based, random sampling program is recommended for non-suspect lots. Any of the following types of sampling can be used.

a. Stratified Random Sampling

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 program. A useful alternative sampling design is stratified random sampling which separates population elements into non-overlapping groups, called strata. Then 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 natural strata because of 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

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 random sampling, when there is reliable information on product volumes to be used to determine the sampling interval that will provide the desired number of samples over time. If the sampling system is too predictable, 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

In biased or estimated worst case sampling, the investigator should use their own judgment and experience regarding the population, lot, or sampling frame to decide which samples to select. As a non-random technique, no inferences should be made about the population sampled based on data collected. The population group anticipated to be at greatest risk may be identified.

Exporting countries should conduct a comprehensive residue testing program and provide results to importing countries. Based on an importing country's data, testing may be conducted as applied to non-suspect products. Countries which do not provide residue testing results showing compliance with MRLVD's should be sampled as suspect lots.

6.5 Preparation of the Bulk Sample

The bulk sample is prepared by combining and thoroughly mixing the primary samples.

6.6 Preparation of the Final Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from the primary sample by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some National legislation may require the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Samples

a. Each sample or subsample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged 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°C, immediately after collection, and packed in a suitable container that retards thawing. If possible, the shipping container should be placed in a freezer for 24 hours prior to packing and shipping the frozen sample.

7. **Records**

Each sample must be correctly identified by a record with the type of sample, origin of the sample (e.g., country, state, or town), location of collection of the sample, 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**

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

APPENDIX B

MILK, EGGS AND AQUATIC ANIMAL PRODUCTS

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
I. Group 033 (Mammalian Products - Milks)		
A. Fluid Milk Products		
1. Retail containers	Randomly collect subsamples according to sampling schedule. Subsample size will be 1 retail unit. When the retail unit is less than 0.5 kg then collect 2 units per subsample.	0.5 kg
2. Bulk tank trucks	Agitate product in truck then collect 0.5 liter from each bulk tank.	0.5 kg
B. Manufactured Dairy Products		
1. Concentrated liquid milk products	Randomly collect subsamples according to sampling schedule. Subsample size will be 1 retail unit, except when the retail unit container size is less than 0.5 kg, then collect 2 retail units per subsample.	0.5 kg
2. Dried milk products, cheese, ice cream, and related dairy products	Use sampling schedule to determine sample size. For containers of 0.5 kg or less or 0.25 liter or less, collect a minimum of 2 units per subsample. For containers of 0.5 to 10 kg select 1 unit per subsample. For containers of 10 kg or more collect 1 kg from each unit sampled.	0.5 kg

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
II. Group 039 (Eggs and egg products)		
A. Liquid and frozen eggs	Use sample schedule. Subsample size will be 0.25 liter liquid or 0.5 liter packed shavings from aseptic drillings into containers.	0.5 kg
B. Dried egg products	Use sample schedule. Use same subsample sizes as 1.b. Dried milk products. Collect with aseptic technique.	0.5 kg
C. Shell eggs		
1. Retail packages	Use sample schedule. Subsample size is 1 dozen.	0.5 kg or 10 whole eggs
2. Commercial cases	For 15 cases or less collect 1 dozen from each case, minimum of 2 dozen eggs. For 16 or more cases collect 1 dozen from 15 random cases.	0.5 kg or 10 whole eggs
III. Class B - Type 08 (Aquatic Animal Products)		
A. Packaged fish, fresh, frozen, smoked, Cured, or shellfish (except oysters)	Collect 12 subsamples randomly. Mimimum subsample size is 1 kg.	1.0 kg
B. Bulk fish 0.5 - 1.5 kg.	Collect 12 subsamples randomly. Each subsample should total 0.5 kg of edible fish.	1.0 kg
C. Bulk shellfish (except oysters)	Collect 12 subsamples randomly.	1.0 kg
D. Other fish and shellfish products (including oysters)	Collect 12 - 0.25 liter subsamples.	1.0 kg

COMMODITY	INSTRUCTIONS FOR COLLECTION	MINIMUM QUANTITY REQUIRED
IV. Class E - Type 17 (Derived Edible Products of Aquatic Animal Origin)		
A. Canned fish and shellfish products (except oysters)	Collect 12 subsamples of 5 cans per subsample.	1.0 kg
B. Other fish and shellfish products - fish flour and meal	Use sample schedule. Collect 1 kg per subsample.	1.0 kg

ANNEX C

SAMPLING FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN HONEY

1. Objective

To provide instructions for sampling a lot of honey to determine compliance with Codex maximum residue limits (MRLVDs) for residues of veterinary drugs.

2. Definitions

2.1 Lot

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

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

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

The combined total of all the primary samples taken from the same lot.

2.5 Final sample

The bulk sample or a representative portion of the bulk sample to be used for control purposes.

2.6 Laboratory sample

The sample intended for laboratory analysis. A whole primary sample may be used for analysis or the sample may be subdivided into representative portions, if required by national legislation.

3. **Commodities to which the Guideline Applies**

3.1 Selected according to origin

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

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

3.2 Selected according to mode of processing

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.

Extracted honey that is obtained by centrifuging decapped broodless combs.

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

4. **Principle Adopted**

For purposes of control, the maximum residue limit (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 none of the laboratory samples contain a residue greater than the MRLVD.

5. **Employment of Authorized Sampling Officials**

Samples must be collected by officials authorized for this purpose.

6. **Sampling Procedures**

6.1 Product to Sample

Each lot to be examined must be sampled separately.

6.2 Precautions to take

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 laboratory sample not representative of the bulk or final sample.

6.3 Collection of a Primary Sample

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 Annex C, 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 primary 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

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 violations of the MRLVD, by evidence of contamination during transport or by the availability of other relevant information to the 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

The primary sample is prepared by using guideline 6.1.3 in the Codex Alimentarius Volume III, Codex Standards for Sugars (including Honey), First Edition.

6.6 Preparation of the Laboratory Sample

The primary sample should, if possible, constitute the final sample. If the primary sample is too large, the final sample may be prepared from it by a suitable method of reduction.

6.7 Preparation of the Laboratory Sample

The final sample should be submitted to the laboratory for analysis. If the final sample is too large to be submitted to the laboratory, a representative subsample should be prepared. Some National legislation may require that the final sample be subdivided into two or more portions for separate analysis. Each portion should be representative of the final sample. Precautions in paragraph 6.2 should be observed.

6.8 Packaging and Transmission of Primary Samples

a. Each primary sample should be placed in a clean, chemically inert container to protect the sample from contamination and from being damaged 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.

7. Records

Each primary sample 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

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

Collect 250 ml of liquid or strained honey as described in Codex Alimentarius Volume III, First Edition, section 6.1.3.1.

9.2 Comb honey

Collect 250 ml of liquid honey by cutting across the top of the comb and separate completely from the comb by straining as described in Codex Alimentarius Volume III, First Edition, section 6.1.3.2.

Appendix VIII
Part II

GENERAL CONSIDERATIONS ON ANALYTICAL METHODS FOR RESIDUE CONTROL

It would be ideal to have analytical methods available for determining compliance with MRLVDs that are effective and practical to detect, quantify, and identify all residues of veterinary drugs and pesticides (used as veterinary drugs) that may be present in commodities within the terms of reference of this Codex Committee. These methods could be routinely used by regulatory control authorities of member governments for their residue testing programs to assure compliance with food safety requirements.

Methods with the capabilities mentioned above are not available for many compounds of interest because of the extensive number of potential veterinary drug residues which may find their way into food within the terms of reference of the CC/RVDF. To optimize the effectiveness of regulatory programs to test for veterinary drug residues, residue control programs must use available residue methodology to assure compliance with Codex MRLVDs and, as necessary, take appropriate regulatory action against adulterated products, consistent with the reliability of the analytical data.

To assist regulatory authorities in determining their analytical needs for residue control programs, this paper will describe the types of methods available and a set of attributes which residue control programs may utilize in carrying out their missions.

The principal attributes of analytical methods for residue control programs are specificity, precision, accuracy (measured as systematic error and recovery), and sensitivity. Determining these principal attributes in a method requires well designed multi-laboratory studies. The attributes noted above will be presented in a subsequent section of this paper in more detail.

TYPES OF ANALYTICAL METHODS

Several types of methods are available to food safety agencies and programs to conduct analyses that are consistent with the needs of residue testing programs. Decisions on the use of a specific analytical method depends on the intended objectives of the regulatory program and the analytical performance characteristics of methods.

Methods that are suitable for determining compliance with MRLVDs are those that have successfully completed an extensive multi-laboratory study for specific tissue and species combinations. These methods provide analytical results for

either quantitation or identification that are appropriate to take regulatory action without the need for additional analyses. In some cases, these methods may be considered reference methods, but reference methods frequently are not routine.

Many methods currently being used by residue control programs have successfully completed a multi-laboratory study. Multi-laboratory method performance studies generally satisfy these analytical requirements. Validated methods are those subjected to a properly designed interlaboratory study with three or more analysts, and preferably, in three different laboratories. Collaborative study methods have successfully completed method evaluation in six or more laboratories in an acceptable, statistically designed study. Some residue control methods that have demonstrated their usefulness for determining compliance with MRLVDs have an historical origin. These historical based methods were considered to be the best available at the time of initial regulatory use and have continued in use over an extended period of time in the absence of more effective validated methods.

Collaborative study and validated methods may be extended to additional tissues, species, products, or combinations of these, not included in the original multi-laboratory study by completing additional properly designed laboratory studies. On a case by case basis, analytical results from method extension studies may require additional analysis and/or review before reporting results or taking regulatory action.

Methods that have not been validated by traditional interlaboratory study, but provide results that may be correlated and compared with data obtained from a collaborative study or validated method, may serve a regulatory purpose. The validated and non-validated methods must be compared in a statistically acceptable study design using portions of the same (homogeneous) samples prepared for this comparison. The data from these studies should be reviewed by a peer group of regulatory scientists to determine the comparability of method performance.

There are some non-routine veterinary drug residue methods suitable for enforcement of MRLVDs. These methods may not have been subjected to an interlaboratory study because they require specialized expertise or equipment. Good quality control and quality assurance procedures must be applied with these methods. Analytical data obtained from these methods should be reviewed by a peer group of regulatory analysts before recommending any regulatory action. These analytical methods may require analysis by another method to corroborate the initial experimental findings.

Occasionally, a method may be suitable for Codex purposes because the toxicology of an analyte does not allow an MRLVD to be established. Methods for analytes such as chloramphenicol would be in this category. Some methods in this category will include those presented above which are not sufficiently sensitive to quantitate and/or identify analyte(s) at or below the MRLVD. Such methods also may not meet other performance factors stated above.

There are some methods for which additional analysis is required to support regulatory action. This category may include methods that do not provide adequate information of structure or residue concentration. Analytical methods that may have been subjected to ruggedness testing, but not successfully to a multi-laboratory study to evaluate method performance, may have limited usefulness in a residue control program. However, these methods may be useful in non-recurring or infrequent residue analyses, but they commonly require use of a rigorous protocol for sample analysis. Results from such methods should be considered only as estimates of analyte concentration or identification without additional supporting analytical information. Results from these methods can be useful for gathering residue information and determining whether there is a need to develop a more definitive method. These methods should not be used alone for residue control purposes on official samples without additional information (e.g., such as the presence of an injection site in the sample).

Certain methods may only be suitable for determining whether or not a veterinary drug residue problem exists in a sampling population. Methods in this category are used for information gathering, or exploratory residue control studies. Exploratory studies may also be undertaken using methods which have not been subjected to interlaboratory study. These non-routine methods may be complex, or require highly specialized instrumentation, and may have been developed and used only in a single laboratory. Analytical results from these methods should not be used independently for taking regulatory action, but may be used to determine the need for additional testing and/or development of a method suitable for routine enforcement of MRLVDs.

Methods designed to analyze large numbers of samples quickly may be useful for determining the presence or absence of one or more compounds in a quantitative or semi-quantitative manner, at or above a specified concentration. Results at or above the MRLVD commonly require additional analysis using a method with acceptable performance characteristics before taking regulatory action. Results from methods of this type that are below the MRLVD but above a level of reliable measurement of a more definitive method, may have limited use in determining exposure patterns.

METHOD DEVELOPMENT CONSIDERATIONS

Developing an analytical method requires analysts, laboratory space, equipment, and financial support. To optimize the benefit of these resources, it is important to provide introductory and background information to establish a perspective for planning an analytical method development project, and for evaluating the performance of the analytical method.

Residue control programs should use methodology suitable to the analytes of interest to assure a safe and wholesome food supply. Necessary and appropriate regulatory action should be taken against adulterated products, consistent with the reliability of the analytical data. Before initiating method development activities, the intended use and need for a method in a residue control program should be established. Other considerations include the compound or class of compounds of interest (and potential interfering substances), potential measurement systems and their properties, the pertinent physical and chemical properties that may influence method performance, the specificity of the desired testing system and how it was 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 items, and any other specific information pertinent to program needs.

ANALYTICAL PERFORMANCE CHARACTERISTICS

Specificity is the ability of a method to distinguish between the analyte of interest and other substances which may be present in the test sample. A residue control method must be able to provide unambiguous identification of the compound being measured. The ability to quantitatively differentiate the analyte from homologues, analogues, or metabolic products under the experimental conditions employed is an important consideration of specificity.

Precision of a method is the closeness of agreement between independent test results obtained from homogeneous test material under the stipulated conditions of use. Analytical variability between different laboratories is defined as reproducibility, and variability from repeated analyses within a laboratory is repeatability. Precision of a method is usually expressed as 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. Method variability achieved in the developing laboratory after considerable experience with a method, is usually less than the variability achieved by other laboratories that may later also use the method. For this reason, analytical data from a method should be statistically analyzed by procedures described by Youden and Steiner

(Ref: Statistical Manual of the AOAC, Association of Official Analytical Chemists, Arlington, VA, 1975) before preparing a final method write up. If a method cannot achieve a suitable level of performance in the developing laboratory, it cannot be expected to do any better in other laboratories.

Accuracy refers to the closeness of agreement between the true value of the analyte concentration and the mean result that is obtained by applying the experimental procedure a large number of times to a set of homogeneous samples. Accuracy 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. Generally, the accuracy at and below the MRLVD or level of interest must be equal to or greater than the accuracy above the level of interest.

The percent recovery of analyte added to a blank test sample is a related measurement that compares the amount found by analysis with the amount added to the sample. 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). At relatively high concentrations, analytical recoveries are expected to approach one hundred percent. At lower concentrations and, particularly with methods involving a number of steps including extraction, isolation, purification, and concentration, recoveries may be lower. Regardless of what average recoveries are observed, recovery with low variability is desirable.

The sensitivity of a method is a measure of its ability to detect the presence of an analyte and to discriminate between small differences in analyte concentration. Sensitivity also requires the ability to differentiate between analyte, related compounds and background interferences. For analytical instruments used in residue analysis, sensitivity is determined by two factors: instrumental response to the analyte and background interference, or instrument noise. Response is measured by the slope of the calibration curve with analyte standards at concentrations of interest. An ideal situation would be afforded by a linear curve. Instrument noise is the response produced by an instrument when no analyte is present in the test sample.

There are a number of collateral attributes suitable for analytical methods for regulatory control programs beyond these principle method attributes. Methods should be rugged or robust, cost effective, relatively uncomplicated, portable, and capable of simultaneously handling a set of samples in a time effective manner. Ruggedness of a method refers to results being relatively unaffected by small deviations from the optimal amounts of reagents used in the analytical method, time factors for extractions or reactions, or temperature. This does not provide latitude for carelessness or haphazard techniques. Cost-effectiveness is the use of relatively common reagents, instruments, or equipment customarily available and used in a laboratory devoted to veterinary drug residue analyses. An uncomplicated method uses simple, straightforward mechanical or operational procedures throughout the method.

Portability is the analytical method characteristic that enables it to be transferred from one location to another without loss of established analytical performance characteristics.

The capability of a residue control method to simultaneously analyze a set of samples aids in method efficiency by allowing sets or batches of samples to be analyzed at the same time. This attribute reduces the analytical time requirements of sample analysis. It provides, for example, the capability of completing four or more analyses in a normal working day. This is important when large numbers of samples must be analyzed in short or fixed time frames.

Establishing method performance attributes is very important. These attributes provide the necessary information for food safety agencies to develop and manage their public health programs. 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.

INTEGRATING ANALYTICAL METHODS FOR RESIDUE CONTROL

Residue control and standard setting organizations have different terminologies to describe application of analytical methods. Methods for analysis of veterinary drug residues in foods must ultimately be able to reliably detect the presence of an analyte of interest, determine its concentration, and correctly identify the analyte at and above an established maximum residue limit (MRLVD) for regulatory enforcement actions to be taken. The latter methods would be classified as confirmatory methods. These confirmatory methods may or may not have a quantitative or semi-quantitative component.

Other types of methods that may be used in residue control programs, and which can strengthen such a program, may be classified into two additional categories. These categories are quantitative methods and screening methods. Quantitative methods provide precise information concerning the amount of an analyte that may be present, but may only provide indirect information about the structural identity of the analyte. Screening methods may quickly determine the presence of one or more compounds, based upon one or more common characteristic of a class of veterinary drugs in a qualitative or semi-quantitative manner at a specified concentration limit. They may also determine that an analyte is below the limit of detection of the screening method.

These three categories of methods, confirmatory, quantitative, and screening, often share a common set of performance characteristics described above. In addition, they may have other specific considerations. Understanding the relationship between these three categories of methods is important in the development and operation of a balanced residue control program. Screening methods are useful because they provide greater analytical efficiency (i.e., a greater number of analyses may be performed in a given time-frame) than quantitative and/or confirmatory methods. In many circumstances screening methods can be performed in non-laboratory environments. Screening methods suitable for use in non-laboratory environments may be less expensive for regulatory control programs than conducting all testing within a laboratory setting. Screening methods can be to separate test samples with no detectable residue from those that indicate the presence of a veterinary drug residue at or below an MRLVD or an appropriate level of interest. This would allow a laboratory to focus more of its efforts on quantitation of the presumptive positive test samples of regulatory interest.

Screening tests may also be used efficiently in a laboratory setting because they analyze a larger numbers of samples in a given time frame than their corresponding quantitative methods. The cost savings may not be as great as when screening methods are used in non-laboratory environments because the costs associated with the handling and shipping of samples must still be incurred. Presumptive positive results obtained from laboratory screening methods should not be used independently in taking regulatory action. Data obtained from such methods may be used to determine the need for additional testing and/or the development of a method suitable for routine enforcement of MRLVDs.

METHOD DEVELOPMENT AND VALIDATION CONSIDERATIONS FOR RESIDUE CONTROL METHODS

The multi-laboratory method validation study is the most important factor in providing analytical data to define method performance characteristics.

In developing a residue control method, whenever possible, data should be collected from three types of samples. 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. Dosed or biologically incurred tissue, from food producing animals and birds that have been treated with the drug, provide additional analytical performance information about biological or other interactions that may occur when analyzing residue control samples.

Residue methods should be designed with as much simplicity as possible. Analytical simplicity helps minimize the variety, size, and type of glassware and equipment needed, minimizes the potential for analytical errors, and reduces laboratory and method costs. Reagents and standards must be commercially available or available from some other reliable source. Instrumentation should be selected based on its performance characteristics rather than a particular manufacturer.

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. 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.

Residue control methods that may be subjected to widely variable physical test environments will place some additional requirements on methods. Addressing these 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 lenient. Cooler environments may require reagents and solvents to have different physical properties, such as lower freezing point and greater solvating characteristics, to ensure 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 color 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.

An analytical method developed and used in only one laboratory may have limited use in a residue control program. The reliability of reported values may be a concern even though strong quality control procedures may have been employed. As a minimum, three laboratories expected to use these methods should be used to develop performance characteristics for residue control, including analytical variability, and obtain statistically acceptable agreement on the same samples divided among the testing laboratories. Methods with higher reliability for residue testing should be able to successfully undergo a collaborative study involving at least six different laboratories (ref: Use of Statistics to Develop and Evaluate Analytical Methods (by G.T. Wernimont and W. Spendley, Association of Official Analytical Chemists, Arlington, VA), and Compound Evaluation and Analytical Capability National Residue Program Plan 1990, (section 5, USDA, Food Safety and Inspection Service, Washington, D.C.).

The principles for conducting either a validation or collaborative study of a residue control method are the same. Samples for evaluating method performance should be unknown to the analyst, contain the residue near the MRLVD as well as samples with the analyte above and below the level of interest, and test material blanks. All study samples should be analyzed over a limited number of days, preferably with replicate analysis, to improve statistical evaluation of method performance. It should be noted that these are only minimal requirements. Duplicate analyses in only six laboratories with one or two animal species and tissues would yield limited quality estimates for repeatability and reproducibility.

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 program is performing in an acceptable manner. Quality control and quality assurance programs are invaluable to support decision-making for residue control agencies, improving the reliability of analytical results, and providing quality data for residue control programs to demonstrate food safety to consumers, producers, and law making bodies regarding residues of veterinary drugs in food.

Appendix VIII
Part III

ATTRIBUTES OF ANALYTICAL METHODS FOR RESIDUES OF VETERINARY DRUGS IN FOODS

The performance characteristics of analytical methods for determining compliance with MRLVDs must be defined and proposed methods evaluated accordingly. This will ensure reliable analytical results and provide a secure basis for determining residues of veterinary drugs in foods for commodities in international trade. The accompanying paper, General Considerations of Analytical Methods for Regulatory 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 three categories of methods for determining compliance with Codex MRLVDs referred to as Level I, Level II and Level III methods will be presented followed by additional attributes that are applicable to only one or two categories of methods.

(Note: This paper contains numerous definitions. The *Ad Hoc* Working Group on Methods of Analysis and Sampling for CCRVDF has attempted to harmonize these definitions with those provided in the Codex Alimentarius Commission Procedural Manual. In addition, the Canadian Delegation to the CCRVDF has been assigned to develop suitable definitions. When appropriate, these definitions have been incorporated.

GENERAL CRITERIA FOR ATTRIBUTES

All methods may be characterized by a set of attributes or properties that determine their usefulness: specificity - what is being measured; precision - the variability of the measurement; and systematic error or bias - measured as analytical recovery. Another attribute, accuracy, usually refers to the closeness of agreement, or trueness of an analytical result, between the true value and the mean value obtained by analyzing a large number of samples of the test material. For semi-quantitative methods and screening methods, accuracy may also be defined as a measure of false negative and false positive responses. The limit of detection, method sensitivity, practicality of use, tissue/species applicability, limit of detection, and limit of quantitation are additional attributes that have varying relevance to some methods, depending upon the intended use of the analytical results.

Methods may be described according to performance attributes as an alternative to classifying them by intent of use or purpose. This alternative approach defines methods by the analytical information and detail provided concerning the amount and nature of the analyte(s) of interest. Level I methods are the most definitive, while Level III methods usually provide general

information about the presence of an analyte and semi-quantitative information about the amount of material present.

Level I methods quantify the amount of a specific analyte or class of analytes and positively identify the analyte, providing the greatest amount of reliability for quantitation and structure identification of the analyte at the level of interest. These methods may be a single procedure that determines both the concentration and identity of the analyte, or a combination of methods to quantify and confirm the structure of a veterinary drug residue. A good example of the latter is a chromatographic technique combined with a mass spectrometry procedure. 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.

Level I methods may be limited to analytes with appropriate physical and chemical properties amenable to chromatographic and other instrumental methods of analysis. For example, at the present time, there are very few antibiotic drugs for veterinary use that have mass spectrometric procedures useful to determine compliance with MRLVDs because of the relatively low volatility and stability of antibiotic drugs to chemical techniques commonly employed for mass spectrometry analysis. However, new technology and instrumentation is now making development of these confirmatory methods possible. Level I methods are sometimes referred to as reference methods.

Level II methods commonly determine the concentration of an analyte at the level of interest, but do not provide unequivocal structure identification. These methods may use structure, functional group, or immunological properties as the basis for the analytical scheme. A common practice is to use one level II method as the determinative assay and a second level II method as the positive identification procedure. These methods may also be used to verify the presence of a compound or class of compounds. Two Level II methods may provide information suitable for a Level I method, when they use different chemical procedures. The majority of analytical methods commonly used to support MRLVDs are quantitative Level II laboratory methods.

Level III methods are those that generate less definitive but useful information. These testing procedures generally determine the presence or the absence of a compound or class of compounds at some designated level of interest. They are often based on non-instrumental techniques. For these reasons, Level III methods are commonly referred to as screening or semi-quantitative methods. Results on a given sample are not as reliable as Level I or II methods and usually need corroborating information for regulatory action. For example, Level III methods may provide good semi-quantitative information, but poor identification. Alternatively, they may provide strong or unequivocal identification with very little quantitative information. Level III methods are not poorly described or sloppy methods. They must have a well-defined operating protocol, operating characteristics and performance data.

Many of the microbiological agar plate assay procedures, enzyme inhibition assays and immunology based systems are in this category. They are useful for residue control programs because of their high sample capacity, portability, convenience and potential suitability to non-laboratory environments. The limitation of Level III type methods is that action based on individual positive results usually requires verification using Level I or II methods. Individual results may be verified by epidemiological information.

Level III methods may offer substantial advantages to a residue control program. Their advantages include analytical speed, sample efficiency through batch analysis, portability to non-laboratory environments, good sensitivity, or the ability to detect classes of compounds. Even though a Level III method may not detect a specific compound at a regulatory limit (i.e., an MRLVD) with every

sample, it may be better than relying on Level I and II methods because of their ability to test more samples.

The decision to use Level III methods should be determined in part by performance characteristics, as well as the need to test large numbers of samples within a given time frame. Two key characteristics to consider for Level III methods are the percent false positives and percent false negatives, determined by comparison with a validated quantitative assay in a statistically designed protocol. The percent false negatives must be quite low at the levels of interest, while slightly more flexibility may be acceptable for false positives. Residue detection limits can be described based on these two parameters.

METHOD ATTRIBUTES

Specificity is the ability of a method to distinguish between the analyte being measured and other substances which may be present in the test material. A proposed method also must provide the required specificity for the compound being measured and discriminate between other structurally similar substances. This characteristic is predominately a function of the measuring principle or detection system used. Certain instrumental techniques such as Fourier transform infrared spectroscopy or mass spectrometry may be sufficiently specific by themselves to provide unambiguous identification. These are often referred to as confirmatory methods. Positive identification from a confirmatory method is usually considered necessary before regulatory action is taken in those instances when an analytical result is not sufficiently specific for regulatory purposes. Confirmatory methods may be considered Level I methods when they provide a determinative result to quantify and tentatively identify a given analyte, and a procedure which verifies the identity of the analyte of interest.

Other techniques, when they are used in combination, may be capable of achieving a comparable degree of specificity as confirmatory techniques. For example, specificity 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. Such procedures must be applicable at the designated maximum residue limit (MRLVD) of the analyte.

The specificity of a screening method normally is not as great as that of a determinative method, because screening methods often take advantage of a structural feature common to a group or class of compounds. These methods generally fit into the Level III methods category. Techniques based on biological assays, immunoassays, or chromogenic responses are not expected to be as specific as those techniques which unequivocally identify a compound. Specificity of a screening method may be increased by the use of chromatographic or other separation technique.

If a non-specific response or some ambiguity in a test result is obtained (i.e., cross-reactivity with components of the matrix other than that for which the analysis was designed), studies that approximate the concentration of the non-specific response of the analytical method may be required to identify the compounds that respond to the detection system. If the method is not sufficiently specific, then a confirmatory or identification procedure will be needed to characterize the analyte of interest.

Precision is an important performance characteristic of residue control methods. This attribute is common to all methods, and as noted below, acceptable precision may not be a function of the type of method, but of the concentration of the analyte in the original sample. There are several types of precision. Inter-laboratory precision, or reproducibility, is the closeness of agreement between test results obtained with the same method on identical test material in different laboratories. The variation in replicate analyses of a test material within a laboratory when performed by one analyst is repeatability. The intra-laboratory

variability among analysts performing the same analysis is within-laboratory bias, and is primarily due to random error. Precision is usually expressed as a standard deviation (an absolute value determined experimentally). More useful is the relative standard deviation, or coefficient of variation. This parameter expresses variability as a function of concentration, and is relatively constant over a given concentration interval.

Precision limits for analytical methods, as a function of concentration, are presented below. The recommended values take into consideration the wide variety of methods, analytes, matrices, and species within the terms of reference of the Committee and that are usually applied in a broad-based residue control program.

Concentration	Coefficient of Variability (CV) (Repeatability)
≤ 1 ug/kg	35%
≥ 1 ug/kg ≤ 10 ug/kg	30%
≥ 10 ug/kg≤ 100 ug/kg	20%
≥ 100 ug/kg	15%

The variability achieved in the laboratory where a method was developed, and where there is considerable experience, is usually smaller than that attained by laboratories that may later use the method and have less experience with it. The final version of the method should be optimized by using procedures such as ruggedness testing to identify its critical control points and ensure that its performance will not be adversely affected by small changes in using the analytical procedure. If a method cannot achieve acceptable performance in the sponsor's laboratory, its performance usually will not be any better in other laboratories.

When developing analytical data to be used to define expected method variability and other performance characteristics, methods should be performed by an analyst who has not been directly involved in developing the method. This procedure will verify the adequacy of the method's written description and help identify critical parameters which affect method performance.

The within laboratory coefficient of variation should be ≤15 percent when the designated concentration of the analyte is greater than or equal to 100 ug/kg. When the designated concentration of the analyte is 10 - 100 ug/kg, the within laboratory coefficient of variation should be ≤20 percent. When the concentration of interest is below 10 ug/kg, a coefficient of variation of ≤30 percent is acceptable.

A Level III method should be capable of identifying samples that contain a residue concentration at the level of interest. When a sample contains a residue that exceeds the MRLVD using a semi-quantitative (screening) method, regulatory action requires additional analysis. In this situation, the sample will require analysis using a determinative method and a confirmatory method with defined performance characteristics. A useful attribute for Level III methods is its precision at and just below the MRLVD. Precision may be somewhat less important above the MRLVD.

Systematic error, or method bias, is the difference between the experimentally determined (measured) value and the mean result that would be obtained by applying the experimental procedure a very large number of times to the test material. Systematic errors are always of the same sign and magnitude. Random error, however, is variable in magnitude and sign and the mean of random errors may approach zero if sufficient samples are tested. Accuracy is generally expressed as the percent recovery of the analyte of interest. Recovery is obtained experimentally by adding known quantities of the analyte directly to separate portions of the test material and comparing the amount recovered with the amount added. The percent recovery of an analyte added directly to the sample matrix is generally a higher value than is obtained experimentally when isolating the same

biologically incurred analyte from a given sample matrix. At relatively high analyte concentrations, recoveries are expected to approach 100 percent. At lower concentrations or with multi-step methods that require extractions, solvent transfers, concentration steps, and absorption chromatography, recoveries will be lower. Variability of analyte recovery is usually as important as the percent recovery itself and should be small.

Average recoveries of 80 to 110 percent should be obtained when the MRLVD for the analyte is 100 ug/kg or greater and when the analytical method can be performed with acceptable precision.

Recommended acceptable recoveries at lower MRLVDs are 70 to 110 percent when the MRLVD is 10 ug/kg to 100 ug/kg, and 60 to 120 percent when the MRLVD is less than 10 ug/kg. These recovery limits are reasonable when viewed within the context of the wide variety of residues, methods, matrices, and species normally included in a broad-based residue testing program. Variability in recovery should be small regardless of the percent recovery.

Correction factors for more or less than 100 percent recovery may be appropriate when analytical methods use isotope dilution procedures or other appropriate internal reference standards for quantitation purposes.

The accuracy requirements of different types of methods will vary with the intended use for the results. In general, methods should have their greatest accuracy at the MRLVD. The accuracy requirements of confirmatory methods may not be as great as is required for quantitative methods, because in most residue control programs these methods are only performed after a residue concentration greater than the MRLVD has been determined by a quantitative method. Most confirmatory methods have a quantitative aspect built into them which serves as an additional check on the previously performed quantitative method. Suggested accuracy requirements for methods are given below, and are based upon the previously stated considerations of a broad-based residue testing program.

Concentration	Acceptable Range
$\leq$1 ug/kg	-50 to +20%
$\geq$1 ug/kg $\leq$ 10 ug/kg	-40 to +20%
$\geq$10 ug/kg $\leq$ 100 ug/kg	-30 to +10%
$\geq$100 ug/kg	-20 to +10%

Level III methods may be useful for residue control programs in several scenarios. For example, they may be used in situations where no MRLVD can be established or where one does not otherwise exist, and regulatory action may be taken if any amount of the drug residue is found. Non-quantitative methods may also be used when the MRLVD or the level of interest is less than the limit of detection of the screening method. In both cases, it is necessary to evaluate proposed methods for the specified residue test to experimentally determine the lowest concentration at which an analyte can be detected and to determine method accuracy and limits by using data on false negatives (i.e., a negative analytical result is obtained when the analyte is present), and false positives, (i.e.,a positive result is obtained when the analyte is not present) at or above the MRLVD.

If Level III methods involve a manufactured test kit, at a minimum, the accuracy, precision, specificity and lowest detection limit data should be provided by the manufacturer. The users should verify the validity of this data through their own studies and evaluate performance by quality control checks. The lowest detectable concentration of an analyte should represent the smallest amount of an individual analyte that can be reliably observed or found in the test sample. The method accuracy, expressed in terms of false negatives and false positives, should be determined by a statistically valid, scientifically correct study with appropriate controls.

In general, non-quantitative methods should produce less than 5 percent false negatives and less than 10 percent false positives when analysis is performed on the test sample. These values may vary depending on the type of action that will be taken as a result of the analytical test. Conservative values should be chosen appropriate to residue testing needs.

The limit of detection is the smallest measured concentration of an analyte from which it is possible to deduce the presence of the analyte in the test sample with acceptable certainty. This determination should consider matrix related interferences with an instrumental signal to noise (S/N) ratio greater than 5:1 or the concentration determined by a factor of 3 standard deviations of the signal response for blank tissue, whichever is less.

Sensitivity is a measure of the ability of a method to detect the presence of an analyte and to discriminate between small differences in analyte content. This may be determined by the slope of the standard curve at concentrations of interest.

COLLATERAL PARAMETERS FOR METHODS SUITABLE FOR ROUTINE USE FOR ENFORCEMENT OF MAXIMUM RESIDUE LIMITS

Residue control methods should be capable of analyzing several samples simultaneously, normally in groups of four or more during a normal work period. These methods should ideally require no more than about 2 hours of analytical time per sample. This does not require that results for a set of analytical samples must be completed within 2 hours. Several hours may be necessary to prepare a set of extracts or complete a microbiological incubation, for example, before analysis of test sample results can be completed. Regulatory methods should be able to be completed within reasonable time periods consistent with regulatory objectives.

The applicability of a method refers to the tissue matrices and animal species that a particular method has demonstrated acceptable method performance for compliance with an MRLVD.

The limit of quantitation corresponds to the smallest measured concentration of residue from endogenously incurred test material above which a determination of the analyte can be made with a specified degree of certainty to its accuracy and precision.

For determining compliance with an MRLVD, an analytical method should require only instrumentation generally available in a laboratory devoted to trace analyses in the appropriate test material. The methods should be capable of analyzing analytes at or below the MRLVD. In addition, the methods should have written protocols that include extensive quality assurance and quality control components. These quality assurance plans should also include analyst training needs.

Whenever applicable, methods should be evaluated in an interlaboratory study using some test samples with biologically incurred analyte. Experience suggests that using biologically incurred residues for method evaluation provides a better description of the exprcted performance characteristics of the method as it would be used routinely by regulatory authorities.

Residue testing methods must demonstrate that they can be performed at their described performance characteristics by experienced analysts who have received adequate method training. Acceptable methods performance can be demonstrated by successfully analyzing sets of samples containing the analyte of interest in sample matricies within the scope of the CC/RVDF terms of reference.

Methods to determine compliance with MRLVDs should utilize commercially available reagents and equipment. Methods may become impractical and potentially

unreliable if new or unusual reagents are not readily available. New or unusual reagents and standards must be assured by the method sponsor upon request.

Regulatory methods for residue control should not use large quantities of solvents, reagents, and supplies which would render the method economically impractical. Methods for determining compliance with Codex MRLVDs should be designed for safe performance by trained analysts.

Several other indicators of satisfactory performance may be helpful in determining whether or not a method is acceptable for Codex purposes. These include: a) calibration (standard) and analytical (recovery) curves; b) information on the effectiveness of extraction for removing specific potential interferences; c) adequate method sensitivity (slope of the standard calibration curve) with a linear dynamic range at the concentration of interest; d) adequate resolution from matrix components; e) sufficiently low and reproducibly consistent blanks; and f) stability studies performed on the matrix, the analyte within the matrix, and reagents used in the procedure. The analytical response of the blank should be no more than 10% of the analyte response at the MRLVD, whenever an MRLVD is established. Critical control points within the analytical procedure, those steps where extreme care must be taken to insure optimum method performance, and stopping points within the method need to be identified and noted in the written procedure.

SPECIFIC DATA NEEDED

The developer of a method must provide pertinent information and supporting data necessary to familiarize other intended users of a method so they can achieve satisfactory methods performance. This necessary information should include the following:

For Codex methods, the developer of a method should collect and provide data from three types of samples: a) control tissue samples from animals that are known not to have been exposed to the analyte; b) tissue samples that are fortified or spiked at the levels of interest by the addition of known amounts of the analyte to uncontaminated control tissue; and c) dosed or incurred tissue samples at the concentration of interest (MRLVD) obtained from animals treated with the veterinary drug according to good veterinary practices.

Methods provided by developers, drug sponsors and commercially available test kits intended for use with Codex MRLVDs should only be recommended for use after it can be demonstrated that the method(s) will meet established performance characteristics or provide an improvement to current methods, regulatory decision making and regulatory consistency.

The developer of the method must determine a) the analytical response obtained when the matrix is known to be free from chemical interferences; b) the method variability, and c) the lowest concentration at which the amount of analyte present can be detected with reasonable statistical certainty. The data should demonstrate that the proposed method can satisfactorily recover and identify known amounts of the analyte that have been added to the test sample. Finally, the developer should demonstrate that the proposed method can satisfactorily recover the analyte from the target tissue matrix in which it has been biologically bound or incurred. Recovery studies must demonstrate absence of responses from substances that may interfere or adversely affect the reliability of the analysis.

The method must demonstrate acceptable method performance in controlled laboratory environments and in field trials which represent anticipated operating conditions, if that is the intended use of the method. The results must be verified by appropriate quality assurance and quality control procedures, including analysis of known blank and positive control samples. Analysis of sufficient numbers of both positive and negative control samples must be performed to

establish false positive and false negative rates, with a statistically appropriate number of these samples analyzed by a separate method to verify the results.

A complete description of the method must be provided which includes the scientific principle(s) upon which the method is based, preparation of analytical standards, appropriate tissues the method is suitable for, shelf life and storage conditions for the analyte in solution and in the target tissue matrix, reagent and standard shelf life stability, instrumentation as well as their performance standards and calibration procedures, and identification of critical steps and stopping places. Test limitations as well as appropriate and inappropriate uses of the test must be described. Critical test components and reagents must be identified and specifications described. The developer must provide procedures for demonstratlng evidence of satisfactory method performance as well as guarantee the long term availability of all components necessary to successfully perform the test.

For rapid test procedures, the quality control criteria needed to verify and maintain acceptable method performance and to determine that a test kit is operating properly must be provided. Information to verify proper test data interpretation associated with the quality control criteria must be specified. A standard curve prepared for the analyte of interest of known purity is needed. A typical analytical curve prepared by fortifying blank test material with the analyte of interest must be provided.

Data from uncontaminated, fortified, and dosed test material is required to show that the method meets the specificity, precision, systematic error, and accuracy attributes for its intended use. Test samples should be fortified at 0.5 (where practical), 1 and 2 times the MRLVD. Additional samples within these concentration limits may be included.

Data from interlaboratory studies should be provided on the analytical worksheet developed for evaluating methods for Codex MRLVDs. The method should be tested in three or more laboratories for ease in evaluating multi laboratory study reports. Each laboratory should analyze samples fortified as stated previously and should test biologically incurred samples containing the analyte at the same concentrations.

Test kits should utilize simple, unambiguous procedures. The analytical procedures designed into test kits to be used by field personnel should be successfully evaluated by at least ten trained individuals in a properly designed study before being placed into general use. The study environment must be similar to that expected for routine use of the test. The design should provide sufficient data for a statistical description of false positive and false negatives, and allow determination of the analytical limits of the test. Participants should include those individuals who have been trained by the developer of the test to determine that training procedures are sufficient to provide acceptable method performance.

STANDARD REFERENCE MATERIALS FOR VETERINARY DRUG RESIDUE ANALTYSIS

At the present time it is usually not practical to develop standard reference materials for determination of residues of veterinary drugs in foods. There are specific difficulties in developing standard reference materials for international use as noted below.

Scme drugs are not sufficiently stable in test materials at ordinary freezer temperatures. Veterinary drug residue concentrations commonly deplete with time, dependent upon the analyte and test material, at ordinary freezer temperatures. These test materials must be stored and shipped at ultracold temperatures or use lyophilized, irradiated, or treated otherwise to reduce enzymatic activity and prevent loss of analyte. The relevant studies for most compounds of interest to CC/RVDF have not been published at this time, so it is not known whether treatments noted above will affect the extent to which the drugs of interest are bound to the

tissues, whether drug residues remain stable in tissues, or whether they might chemically alter the trace residues.

Recognized standard reference materials are generally very expensive and, considering their other limitations, they are generally not cost effective for residue analysis. Commercial reference standards for veterinary drugs have limited availability at the present time. Because of these and other limitations, such as analytical variability of a method versus the concentration of the analyte (i.e. low mg/kg to ug/kg), standard reference materials are generally inappropriate.

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Appendix IX

DRAFT GLOSSARY OF TERMS AND DEFINITIONS AT STEP 8

Foreword

The Glossary of Terms and Definitions has been elaborated by the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) with a view towards providing information and guidance to the Committee, and is intended for internal Codex use only.

The Glossary is intended to be an open list which is subject to review by the CCRVDF in order to update, modify or add to the list of terms. Relevant terms elaborated by other Codex committees are included.

1. Acceptable Daily Intake (ADI)[3/]: An estimate by JECFA of the amount of a veterinary drug, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk (standard man = 60 kg).

2. Bioavailable Residues[3/]: Those residues that can be shown, by means of an appropriate method (e.g. Gallo-Torres method) to be absorbed into systemic circulation when fed to laboratory animals.

3. Bound Residue: Residues derived from the covalent binding of the parent drug or a metabolite of the drug and a cellular biological soluble or insoluble macromolecule. These residues are not extractable from the macromolecule by exhaustive extraction, denaturation or solubilization techniques. They do not result from the incorporation of metabolized, radiolabelled fragments of the drug into endogenous compounds, or the same macromolecule by normal biosynthetic pathways. Information concerning the calculation of bound residues may be found in Annex 3 of the 34th Report of JECFA (pages 58-61, WHO TRS 788).

4. Egg: Egg (in shell) of domesticated chickens (hens).

5. Extractable Residue[2/]: Those residues extracted from tissues or biological fluids by means of aqueous acidic or basic media, organic solvents and/or hydrolysis with enzymes (e.g. sulfatase or glucuronidase) to hydrolyse conjugates. The extraction conditions must be such that the compounds of interest are not destroyed.

6. Fish: Means any of the cold-blooded aquatic vertebrate animals commonly known as such. This includes Pisces, Elasmobranchs and Cyclostomes. Aquatic mammals, invertebrate animals and amphibians are not included. It should be noted, however, that this term may also apply to certain invertebrates, particularly Cephalopods.

7. Good Practice in the Use of Veterinary Drugs (GPVD)[1/]: Is the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions.

8. Marker Residue[3/]: A residue whose concentration decreases in a known relationship to the level of total residues in tissues, eggs, milk or other animal tissues. A specific quantitative analytical method for measuring the concentration of the residue with the required sensitivity must be available.

9. Maximum Residue Limit for Veterinary Drugs (MRLVD)[1/] is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food.

It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects.

When establishing an MRL, consideration is also given to residues that occur in food of plant origin and-or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available.

10. Meat: The edible part of any mammal.

11. Milk: Exclusively the normal mammary secretion obtained from one or more milkings without either addition thereto or extraction therefrom. The term may be used for milk treated without altering its composition, or for milk the fat content of which has been standardized under domestic legislation. The term may also be used in association with a word or words to designate the type, grade, origin and/or intended use of such milk or to describe the physical treatment or the modification composition to which it has been subjected, provided that the modification is restricted to an addition and/or withdrawal of natural milk constituents. In international trade, the origin of the milk shall be stated if it is not bovine.

12. Muscle[2/]: Muscle tissue only.

13. Non-Extractable Residues[2/]: These residues are obtained by subtracting the extractable residues from the total residues and comprise:

i) Residues of the drug incorporated through normal metabolic pathways into endogenous compounds (e.g. amino acids, proteins, nucleic acid). These residues are of no toxicological concern.

ii) Chemically-bound residues derived by interaction of residues of parent drug or its metabolites with macromolecules. These residues may be of toxicological concern.

14. Poultry: Means any domesticated bird including chickens, turkeys, ducks, geese, guinea-fowls or pigeons.

15. Regulatory Method of Analysis: A method that has been legally enacted and/or validated in a multi-laboratory study and can be applied by trained analysts using commercial laboratory equipment and instrumentation to detect and determine the concentration of a residue of a veterinary drug in edible animal products for the purpose of determining compliance with the MRL.

16. Residues of Veterinary Drugs[1/]: Include the parent compounds and/or their metabolites in any edible portion of the animal product, and include residues of associated impurities of the veterinary drug concerned.

17. Screening Method: A rapid, relatively inexpensive, and rugged field method used for testing for a specific substance or closely related group of substances which are sufficiently selective and sensitive to allow at least

semi-quantitative detection of residues in contents in accordance with the established maximum limit.

18. Temporary Acceptable Daily Intake (TADI)[2/]: Used by JECFA when data are sufficient to conclude that use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. A higher-than-normal safety factor is used when establishing a temporary ADI and an expiration date is established by which time appropriate data to resolve the safety issue should be submitted to JECFA.

19. Tissue[2/]: All edible animal tissue, including muscle and by-products.

20. Tissue, Control: Tissue from animals not treated with veterinary drugs of the same species, sex, age and physiological status as the target species.

21. Tissue, Dosed: Tissue from animals of the test species that have been treated with the drug according to its intended use.

22. Tissue, Spiked or Fortified: Tissue containing known concentrations of the analyte added to the sample of control tissue.

23. Total Residue[2/]: The total residue of a drug in animal derived food consists of the parent drug together with all the metabolites and drug based products that remain in the food after administration of the drug to food producing animals. The amount of total residues is generally determined by means of a study using the radiolabelled drug, and is expressed as the parent drug equivalent in mg/kg of the food.

24. Validated Method: An analytical method which has been subjected to a multi-laboratory study for accuracy, precision, reproducibility performance and ruggedness. Concise written procedures for sample selection, preparation and quantitative analysis are provided for inter-laboratory quality assurance and consistency of results, on which an appropriate regulatory method of analysis can be established.

25. Veterinarian Client-Patient Relationship: The relationship is recognized when the livestock enterprise, premises and husbandry practices are known to the veterinarian as a result of a recent professional visit to the site and the veterinarian is available for emergency on site consultation and is responsible for preventative medicine programs.

26. Veterinary Drug[1/]: Any substance applied or administered to any food-producing animal, such as meat or milk producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic, or diagnostic purposes, or for modification of physiological functions or behaviour.

27. Withdrawal Time and Withholding Time: This is the period of time between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the maximum residue limit for this veterinary drug (MRLVD).

Notes:

1/ These definitions have been adopted by the Codex Alimentarius Commission, and are included in the Codex Alimentarius Procedural Manual.

2/ These definitions have been established and adopted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

3/ These definitions, as previously established and adopted by the Joint FAO/Expert Committee on Food Additives, have been modified by the Codex Committee on Residues of Veterinary Drugs.

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Appendix X

PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION

1. Substances proposed for consideration at the 1993 meeting of JECFA devoted to veterinary drug residues:

Apramycin
Chloramphenicol[1]
Dexamethasone
Enrofloxacin
Flumequine
Isometamidium[1]
Olaquindox[2]
Rafoxamide
Ronidazole[3]
Spectinomycin
Sulfadimidine[4]

2. Substances proposed for consideration at the 1994 meeting of JECFA devoted to veterinary drug residues:

Carazolol[5]
Chlortetracycline
Dihydrostreptomycin
Gentamicin
Imidocarb
Kanamycin
Levamisole[6]
Neomycin
Oxolinic acid
Spiramycin[5]
Streptomycin
Tetracycline

3. Substances scheduled for evaluation at the 1995 meeting of JECFA devoted to veterinary drug residues:

Febantel[7]
Fenbendazole[7]
Oxfendazole[7]

4. Substances of potential interest which may not meet current criteria for evaluation:

Porcine somatotropins

5. Substances not yet scheduled for evaluation:

Phenothiazine
Trimethoprim
Lindane

Footnotes

[1]Company request

[2]Temporary ADI; studies requested for evaluation in 1993 (Thirty-sixth meeting of JECFA, WHO Technical Report Series No. 799, 1990)

[3]Temporary ADI; studies requested for evaluation in 1993 (Thirty-fourth meeting of JECFA, WHO Technical Report Series No. 788, 1989)

[4]Temporary ADI; studies requested for evaluation in 1993 (Thirty-eighth meeting of JECFA, WHO Technical Report Series No. 815, 1991)

[5]Temporary ADI; studies requested for evaluation in 1994 (Thirty-eighth meeting of JECFA, WHO Technical Report Series No. 815, 1991)

[6]Temporary ADI; studies requested for evaluation in 1994 (Thirty-sixth meeting of JECFA, WHO Technical Report Series No. 799, 1990)

[7]Temporary ADI; studies requested for evaluation in 1995 (Thirty-eighth meeting of JECFA, WHO Technical Report Series No. 815, 1991)