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REPORT OF THE MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION

Paris, 26–28 January 2005

The OIE Biological Standards Commission met at the OIE Headquarters from 26 to 28 January 2005. Dr Bernard Vallat, Director General of the OIE, welcomed the Members of the Commission, Prof. Steven Edwards, President, Dr Beverly Schmitt, Vice-President and Dr Anatoly Golovko, Secretary General, and the other participants, Dr Adama Diallo, representing the OIE Collaborating Centre for ELISA[1] and Molecular Techniques in Animal Disease Diagnosis, IAEA[2], Vienna, Austria, and Dr Peter Wright, President of the OIE Ad hoc Group on Nonstructural Protein Tests for Foot and Mouth Disease Diagnosis.

Dr Vallat spoke about coordination between the Codex Alimentarius Commission and the OIE on antimicrobial resistance testing standards. He went on to talk about the need to emphasise the importance of OIE Reference Laboratories and their responsibilities. He welcomed the opportunity to hold a conference for the Reference Laboratories during 2006. He recognised that provision of resources from funders to Reference Laboratories remains an issue. Initiatives such as the forthcoming European Technology Platform for Global Animal Health, funded jointly with industry, could provide one means of support. It aimed to strengthen research capacity through joint projects between the EU, Eastern Europe and developing countries. Another important initiative was the ALIVE programme funded by the World Bank, which could support twinning of laboratories in Africa with specific OIE Reference Laboratories. Finally, Dr Vallat mentioned the need to finalise an approach to the use of nonstructural protein tests for foot and mouth disease, particularly for sheep and pigs.

The Agenda and List of Participants are given at Appendices I and II, respectively.

1. OIE Reference Laboratories and Collaborating Centres

1.1. New applications for Collaborating Centre and Reference Laboratory status:

OIE Collaborating Centre for the Application of PCR[3] Methods for Diagnosis of Viral Diseases in Veterinary Medicine

National Veterinary Institute, 751 89 Uppsala, Sweden.
Tel.: (+46.18) 67.18.67; Fax: (+46.18) 67.46.69; E-mail: sandor.belak@sva.se
Designated Reference Expert: Prof. Sándor Belak.

1 ELISA: enzyme-linked immunosorbent assay
2 IAEA: International Atomic Energy Agency
3 PCR: polymerase chain reaction

The OIE Reference Laboratory for the Application of PCR Methods for Diagnosis of Viral Diseases in Veterinary Medicine, Uppsala, Sweden, had requested that its remit be changed to that of an OIE Collaborating Centre. The Commission recommends the adoption of this proposal.

The Commission recommends acceptance of the following new applications for OIE Reference Laboratory status:

OIE Reference Laboratory for Campylobacteriosis (*joint designation*)
Animal Sciences Group (ASG), Division of Infectious Diseases, PO Box 65, 8200 AB Lelystad, The Netherlands
Tel.: (+31-320) 23.81.57; Fax: (+31-320) 23.89.61;
and
Faculty of Veterinary Medicine (FVM), Department of Infectious Diseases and Immunology, PO Box 80.165, 3508 TD Utrecht, The Netherlands.
Tel.: (+31-30) 253.12.42; Fax: (+31-30) 253.31.99;
Designated Reference Expert (for both institutions): Dr Jaap Wagenaar
Email: jaap.wagenaar@wur.nl

It was noted that this Reference Laboratory would cover both bovine genital campylobacteriosis and infections of animals caused by *C. jejuni* and *C. coli.*

OIE Reference Laboratory for Echinococcosis
Laboratory of Environmental Zoology, Department of Biosphere and Environmental Sciences, Faculty of Environmental Systems, Rakuno Gakuen University, Midori-machi 582, Ebetsu 069-8501, Hokkaido, Japan.
Tel.: (+81-11) 386.11.12; Email: fea@cast.hokudai.ac.jp
Designated Reference Expert: Dr Masao Kamiya

1.2. Updating the list of Reference Laboratories

The OIE has been notified of the following changes of experts at OIE Reference Laboratories. The Commission recommends their acceptance:

Foot and mouth disease

Dr G. Matlho to replace Dr M.G. Mosienyane at the Botswana Veterinary Institute, Gaborone, Botswana.

African swine fever

Dr Chris Oura to replace Dr David Paton at the Institute for Animal Health, Pirbright, United Kingdom (UK).

Equine infectious anaemia

Dr Kenji Murakami to replace Dr H. Sentsui at the National Institute of Animal Health, Ibaraki, Japan

1.3. Annual Reference Laboratories report for 2004

Reports had been received from 103/128 Reference Laboratories and 13/14 Collaborating Centres for terrestrial animals. The Commission commented once again on the impressive range of activities by the Reference Laboratories towards the objectives of the OIE, and the continuing support provided by individual experts to the work of the Standards Commission. The full set of reports will be supplied to Member Countries and to all the Reference Laboratories and Collaborating Centres. The international activities relevant to the work of the OIE are summarised in the table:

Reference Laboratories

	General activities	Percentage of Laboratories carrying out these activities
1a)	Diagnostic tests performed	98%
1b)	Agent identification performed	84%
2	Production, testing and distribution of diagnostic reagents	81%
3	Research	81%
	Specific OIE activities	
1	International harmonisation/standardisation of methods	63%
2	Preparation and supply of international reference standards	65%
3	Collection, analysis and dissemination of epizootiological data	62%
4	Provision of consultant expertise	67%
5	Provision of scientific and technical training	66%
6	Organisation of international scientific meetings	28%
7	Participation in international scientific collaborative studies	68%
8	Presentations and publications	83%

Collaborating Centres

	General activities	Percentage of Collaborating Centres carrying out these activities
1	Activities as a centre of research, expertise, standardisation and dissemination of techniques within the sphere of competence	100%
2	International harmonisation of regulations	83%
3	Provision of consultant expertise	58%
	Specific OIE activities	
1	Provision of scientific and technical training	83%
2	Organisation of international scientific meetings	50%
3	Coordination of scientific and technical studies	75%
4	Publications/dissemination of information	92%

1.4. Template for 'twinning' of Reference Laboratories

The Commission is eager to assist laboratories in developing countries to build their capacity with the eventual aim that some of them could become OIE Reference Laboratories in their own right. This would provide a valuable source of additional expertise and laboratory competency in support of OIE objectives. A template was drafted to assist laboratories wishing to make such 'twinning' arrangements. It is attached at Appendix III. The importance of securing funding for individual laboratory developments was emphasised – within Africa the ALIVE programme might be a useful channel.

1.5. International Conference for OIE Reference Laboratories, 2006

Brazil had offered to host a conference for the OIE Reference Laboratories in 2006. The Commission expressed its gratitude to Brazil on behalf of the OIE, and recommends that the International Committee support this proposal as a means of providing a useful channel for interlaboratory collaboration and mutual support.

2. International standardisation of diagnostic tests and vaccines

2.1. OIE standardisation programmes for diagnostic tests

Foot and mouth disease (*FMD*) serology – *Coordinator: Dr D. Paton Institute for Animal Health, Pirbright, United Kingdom*

The OIE Reference Laboratory for FMD in Pirbright, UK, had submitted revised datasheets for the additional bovine reference sera for FMD serology. These complement the existing OIE reference sera by providing reference standards for serotypes O, A, Asia 1, and negative bovine (all seven serotypes). Each of the positives is available as strong positive, weak positive, and cut-off positive. Datasheets are available with further details. All were evaluated by virus neutralisation, liquid phase blocking ELISA, and solid phase competitive ELISA. The Commission commended Dr Paton on this work and adopted the sera as OIE Reference Standards.

FMD non-structural protein (NSP) test – Coordinator: Dr I. Bergmann, Pan-American FMD Center, Rio de Janeiro, Brazil

The OIE Reference Laboratory for FMD in Rio de Janeiro, Brazil, presented data on the characterisation of strong positive, weak positive and negative bovine sera suitable for use as reference sera in the NSP tests for FMD. They had been evaluated by interlaboratory comparisons among the OIE Reference Laboratories, using a variety of NSP protocols. The Commission adopted the sera as OIE Reference Standards for NSP tests.

Dr Bergmann also reported on progress with the establishment of an evaluation panel of 30 sera that should be suitable, once characterised, for evaluating new tests and for harmonisation studies.

Highly pathogenic avian influenza (*HPAI*)

Progress on the joint programme by the OIE Reference Laboratories for HPAI to develop international standard sera for use in the AGID[4] test for this disease had been slowed by their commitments to manage the ongoing problems caused by this disease in SE Asia. The Reference Laboratory in Australia has generously offered to provide characterised sera to other OIE Reference Laboratories for evaluation as potential reference sera and the Commission eagerly awaits the results.

Enzootic bovine leukosis – Coordinator: Dr L Renström, National Veterinary Institute, Uppsala, Sweden

The OIE Reference Laboratory experts for enzootic bovine leukosis from Germany, Sweden and UK had met in Wusterhausen, Germany in October 2004. A report was received by the Commission regarding work in progress on (a) establishment of a new serum standard; (b) establishment of a standard for milk antibody tests (c) establishing a standard protocol for a PCR test (d) identification of future research needs. The Commission looks forward to hearing the outcome of these initiatives.

Dr Knud Pedersen, Director of the Danish Institute for Food and Veterinary Research had confirmed that the existing OIE Reference Serum (widely known as “E4”) is still available from Dr Hoff-Jorgensen at that laboratory.

Caprine arthritis/encephalitis and maedi-visna – Coordinator: Dr C Vitu, AFSSA Sophia Antipolis, France

The OIE Reference Laboratory in Sophia Antipolis, France, had submitted a workplan for the project which was endorsed by the Commission. The industrial partner (Institut Pourquier) had sent a brief progress update.

4 AGID: agar gel immunodiffusion

Porcine brucellosis – Coordinator: Dr K. Nielsen, Canadian Food Inspection Agency, Nepean, Canada

Dr Nielsen has indicated that he would consider distributing reference standard sera along with testing reagents from the index test method, which would allow laboratories to evaluate national standards with the international reference material. The Commission welcomed this initiative.

Caprine and ovine brucellosis – Coordinator: Mrs J Stack, VLA Weybridge, UK

Progress is held up awaiting the procurement of a supply of sera suitable for evaluation as candidate standards.

Equine Influenza – Proposed collaborative study to establish a replacement reference serum

EDQM[5] (formerly European Pharmacopoeia) had informed the OIE of their project, to be run in collaboration with the OIE Reference Laboratory at Newmarket, UK, to develop replacement reference sera for potency testing using HI and SRH methodologies. The Commission welcomed the proposal to establish the serum as OIE Reference material in parallel with their evaluation as EDQM Biological Reference Preparations.

3. List of prescribed and alternative tests

3.1. Rabies ELISAs

The Commission noted a technical report by the OIE Reference Laboratory, Nancy, France, of a multi-laboratory evaluation of the performance of the rabies ELISA (an "Alternative Test") that is described in the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*).

The OIE had also received a validation dossier for a new commercial ELISA kit for rabies serology. This dossier will be evaluated as a pilot under the new OIE guidelines for certification of diagnostic tests.

3.2. FPA[6] for determination of antibody to smooth *Brucella* spp. in sheep and goats

The Commission had received comments from a validation expert on the dossier submitted by The Canadian Food Inspection Agency's Animal Diseases Research Institute in Nepean, Ontario, in support of an application to designate the FPA as a prescribed test for antibody to smooth *Brucella* spp. in sheep and goats. The Commission is seeking further advice from experts before reaching a final decision on whether or not to propose this test for adoption by the International Committee as a prescribed test for trade.

4. Report of the Third Meeting of the Ad hoc Group on Nonstructural Protein Tests for Foot and Mouth Disease Diagnosis

The Commission commended the work of the Ad hoc Group on Nonstructural Protein Tests for Foot and Mouth Disease Diagnosis. The report of the third meeting is given at Appendix IV. The Commission was particularly pleased that the NSP test had been evaluated using the new OIE Template for validation and certification of diagnostic assays (see Appendix III of the Ad hoc group report), and was pleased to endorse the inclusion of this test as fit for the purposes described in paragraph 2.2 of the Ad hoc Group report.

5 EDQM: European Directorate for the Quality of Medicines
6 FPA: Fluorescence polarisation assay

5. Report of the Meeting of the Ad hoc Group on Biosafety/Biocontainment Standard

The Commission noted the report of the meeting of the Ad hoc Group on Biosafety/Biocontainment Standard, whose work is ongoing. The report is given at Appendix V.

Subsequent to the BSC meeting, Drs Steven Edwards and Alejandro Schudel attended a WHO meeting in Lyon (3-4 Feb 2005) to discuss biological risks in laboratory environments, with a particular focus on biosecurity. This is related to, but distinct from, biosafety. The Ad hoc Group will be asked to comment on the draft WHO guidelines on laboratory biosecurity with a view to establishing a common framework for WHO, OIE and FAO.

6. Report of the Meeting of the Ad hoc Group on Antimicrobial Resistance

The Ad hoc Group had met in November 2004, and again in January 2005 in parallel with the BSC. The reports of the meetings are given at Appendix VI. The Commission welcomed the work of the Group, but was unable to agree on its proposed definition of "antimicrobial" (paragraph 5 of the November report). The Commission recognises the need for such a definition within the OIE that should also be cognate with those used by Codex Alimentarius and other international bodies. The following modified definition is proposed:

Antimicrobial agents in veterinary medicine refer to naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of micro-organisms). Anthelmintics and substances classed as disinfectants or antiseptics are excluded from this definition.

7. OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*mammals, birds and bees*)

For this agenda item, the Commission was joined by the Consultant Editor, Dr James Pearson. A feedback questionnaire on the 5th edition of the *Terrestrial Manual* had been sent out to all OIE Delegates and Reference Laboratories. The results were analysed. The Commission appreciated the effort and time undertaken by the responders to the questionnaire. The comments will prove helpful in improving future editions of the *Terrestrial Manual*.

Dr Anatoly Golovko (Secretary General of the Commission) reported that a Russian translation of the *Terrestrial Manual* was well advanced. The Commission commended him on this work and requested OIE to make arrangements for validation of the text and printing. The Spanish edition of the *Terrestrial Manual* is available and a French translation is in progress. The Commission requested OIE to investigate the feasibility of a CD-ROM version, as this is likely to be popular with the laboratory user community.

The Commission considered the revised drafts of those chapters identified for urgent revision: The Role of Official Bodies in the International Regulation of Veterinary Biologicals; Guidelines for International Standards for Vaccine Banks (new chapter); Foot and Mouth Disease; Highly Pathogenic Avian Influenza; Contagious Equine Metritis; and Haemorrhagic Septicaemia. In addition, the introductory chapter on sampling methods will be updated to address changes that have been or soon will be made in the IATA[7] regulations. These chapters will be sent to Member Countries for comment soon with a view to proposing them for adoption at the General Session in May 2005. The chapter on avian influenza was considered under two options, depending on whether or not the new *Terrestrial Animal Health Code* chapter on this disease is adopted by the International Committee. As agreed by the International Committee, revised chapters that are approved at the General Assembly will be updated on the website.

The Commission identified chapters needing revision during 2005/06 and also made preliminary plans for the next full edition for publication in 2008.

7 IATA: International Air Transport Association

Comments had been received regarding the requirement in the *Terrestrial Manual* for quality control (QC) of media to be used for *Brucella* spp. isolation in laboratories that do not (for safety reasons) hold stocks of fastidious strains of the organism. A number of laboratories have adopted a pragmatic solution, by using attenuated strains for QC. This is a complex issue and the Commission decided that further consideration was needed.

The Commission took note of the new OIE publication on Livestock Trypanosomosis and their Vectors in Latin America, written by the OIE expert Dr Marc Desquesnes. This provides useful and additional complementary information to the chapters in the *Terrestrial Manual.* Consideration was given to the configuration of the *Terrestrial Manual* chapters, and consultation was made with Dr Touratier, Secretary General of the Ad hoc Group on Non-Tsetse Transmitted Animal Trypanosomoses. It was decided that the current chapter on "Trypanosomosis (tsetse-transmitted)" should be retained, but that the chapter on Surra should be renamed as "*Trypanosoma evansi* infections" (subtitle "including Surra") and moved to the multispecies section of the *Terrestrial Manual.*

8. Validation and certification of diagnostic assays

The Commission discussed the status of the validation template for submission of data for the OIE Registry of Validated and Certified Diagnostic Assays. Following the last meeting in September, the Director General had invited an expert to write an electronic version of the template adopted by the OIE International Committee in May 2003. This expert informed the Commission that work to develop a web-based template was in progress with support from the OIE Collaborating Centre in Vienna. The Commission accepted the suggestion that the OIE Collaborating Centre hold a meeting of a small group of experts to review this web-based template before submitting the final proposal to the OIE. For the time being, a manual template could be used. Mr François Diaz, who has recently been recruited by the OIE to coordinate validation dossiers, was introduced to the Commission. The Commission discussed two pilot submissions and how they would progress through the registry process.

9. Liaison with other Commissions and Groups

- **SCIENTIFIC COMMISSION FOR ANIMAL DISEASES**

9.1. OIE Expert Group on 'Atypical' Bovine Spongiform Encephalopathy (BSE) Cases

The next meeting of the OIE Ad hoc Group on Atypical Bovine Spongiform Encephalopathy (BSE) Cases will be from 17 to 18 March 2005.

9.2. Report of the meeting of the Ad hoc Group on Antigen and Vaccine Banks for Foot and Mouth Disease

The Commission noted the report of the Ad hoc Group. The Group had drafted a new chapter for the *Terrestrial Manual* on Guidelines for International Standards for Vaccine Banks and had updated the vaccine section of the *Terrestrial Manual* chapter on FMD. These documents will be circulated to Member Countries for comment shortly (see also item 7 above).

9.3. Report of the meeting of the Ad hoc Group on Avian Influenza Surveillance

The Commission noted the report of the Ad hoc Group. Proposed changes to the chapter on avian influenza for the OIE *Terrestrial Animal Health Code* (*Terrestrial Code*) and the draft surveillance guidelines will be taken into account in the draft *Terrestrial Manual* chapter on Highly pathogenic avian influenza (see also item 7 above).

9.4. Report of the meeting of the Ad hoc Group on Classical Swine Fever

Concerning the recommendations of the Ad hoc Group on Classical Swine Fever, the Commission determined to contact one of the OIE Reference Laboratory experts with a view to developing a full assessment of diagnostics and vaccine performance for the disease. It was noted that the report of the European Commission's Scientific Committee on Animal Health and Animal Welfare entitled

Diagnostic Techniques and Vaccines for Foot-and-Mouth Disease, Classical Swine Fever, Avian Influenza and some other important OIE List A Diseases provided a useful summary of the state of the art in 2003.

9.5. Report of the meeting of the Ad hoc Group on Epidemiology

The Commission noted the report of the Ad hoc Group. Proposed changes to the draft surveillance guidelines for the *Terrestrial Code* will be taken into account in the draft *Terrestrial Manual* chapter on FMD.

9.6. Report of the meeting of the Ad hoc Group on Country Status Evaluation for Freedom from Rinderpest

The Commission took note of the comments in paragraph 2 of the Ad hoc Group report, concerning the text of the *Manual* chapter on Rinderpest. The Commission reiterated its view that the i-ELISA could have a place as a screening test for rinderpest antibodies, provided that it was backed up with a more specific confirmatory test. It decided that no changes were required to the text of the chapter.

9.7. Report of the meeting of the Ad hoc Group on Tuberculosis

The Commission had received feedback from the Ad hoc Group concerning the lack of information on validation of the tuberculin test, or other tests, in non-bovine species. One of the OIE Reference Laboratory experts will be requested to collate available information, incorporating inputs from the other OIE Reference Laboratories, and make recommendations on further work required, in time for the next meeting of the Commission in Sept 2005.

- **TERRESTRIAL ANIMAL HEALTH STANDARDS COMMISSION**

9.8. Retention of *Terrestrial Manual* chapters for diseases taken off the OIE list of diseases

The Commission met with Dr David Wilson, Head of the OIE International Trade Department. Dr Wilson was informed that the *Terrestrial Manual* already includes chapters on a number of diseases for which laboratory diagnostic standards are important, but which are not included in the *Terrestrial Code.* The Biological Standards Commission therefore plans to retain chapters in the *Terrestrial Manual* for diseases taken off the OIE list of diseases, unless there is no perceivable value in retaining such chapters. It is clear from comments received from Member Countries that the demand, if anything, is for more chapters on laboratory methods, rather than fewer. Dr Wilson agreed with this view.

Dr Wilson was appraised of the Commission's views on the definition of antimicrobials (section 6 above), and also of the outputs of various Ad hoc Groups convened under the authority of the BSC, that had made proposals regarding chapters in the *Terrestrial Code.*

10. Any other business

10.1. Transport of pathogens

Dr James Pearson attended the meeting of the United Nations Sub-Committee of Experts on the Transport of Dangerous Goods, held in Geneva, Switzerland, December, 2004. Dr Pearson presented his report to the Commission.

The concerns expressed in the OIE paper and by many of the Country Representatives resulted in a compromise that should allow the shipment of samples from "normal" (healthy) animals with a minimum of restrictions. Such samples will still require packaging in compliance with the regulations, but they will be labelled as "Exempt Animal Specimens". This will facilitate disease surveillance programmes and testing of animals to qualify them for shipment. The other modifications in the UN Model Regulations on infectious agents discussed at this meeting should not have a significant effect

on OIE Member Countries. It appears that the changes approved at the previous meeting in July 2004 should become effective by April 2005. Timing of other agreed changes is to be clarified but may not be fully effective till January 2007. Chapter I.1.1 of the *Terrestrial Manual* on sampling methods should be updated to include these changes and the other changes that came into effect on 1 January 2005.

The Commission thanked Dr Pearson for his attention to this very complex piece of legislation.

10.2. Conferences organised by IABs[8]

The draft programmes were noted for two upcoming IABs conferences, in conjunction with the OIE, *viz:* Marker Vaccines, in Ames, Iowa, USA (4-6 April 2005); and New Diagnostic Technology in Animal Health and Biologics Control, Saint Malo, France (3-5 October 2005).

10.3. WAVLD[9] meeting in Montevideo – programme and speakers

The Commission drew up a list of suggested speakers for the 7th OIE Seminar on Biotechnology, on the theme of "Application of Biotechnology to Zoonotic Disease Diagnosis" to be held on 17 November 2005 during the WAVLD meeting in Montevideo, Uruguay.

10.4. Biological Weapons Convention

Dr Pearson presented a report on the Biological Weapons Convention (BWC) Meeting that took place in Geneva, Switzerland from 6 to 10 December 2004. The BWC Report strongly supported the role of OIE, FAO and WHO in surveillance, detection, and diagnosis of human and animal disease. They also encouraged States Parties to support the activities of these organisations. This serves as a strong endorsement of the OIE's activities in these areas. They also endorsed the States Parties taking action to investigate and mitigate intentional disease outbreaks but their support of OIE, FAO and WHO action in this area was less definitive. There was strong support of the OIE's role in disease control both officially at the meeting and in discussion with the members of the delegations.

10.5. Commission's Web site and Internet activities

The Commission took note of the new Web site. It was felt this is an important channel for communication of the Commission's activities and it stands ready to provide active support to the OIE on enhancing the content. The Commission was disappointed that due to firewall issues, the OIE is currently unable to establish an interactive discussion group site specifically for the Commission members.

10.6. Synthetic peptide FMD vaccine

The Commission had received information from a commercial company on the development of a synthetic peptide vaccine for FMD. It agreed to send the dossier to the OIE Reference Experts for FMD for comment and advice on how the OIE should respond to, and develop standards for, this new technology.

10.7. Convention on Biological Diversity

The Commission took note of the proposed agenda for the Convention of Biological Diversity meeting in Bangkok, Thailand, 7-11 February 2005. While recognising the importance of this topic, active participation by OIE in the convention was not considered necessary.

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8 IABs: International Association for Biologicals

9 WAVLD: World Association of Veterinary Laboratory Diagnosticians

10.8. WHO papers on Biological Standardization

A paper entitled "Comparison of vials with ampoules for the storage of biological reference materials", submitted to the WHO Expert Committee on Biological Standardization on 15-18 November 2004, provided useful technical information on different approaches to lyophilisation of biological reference materials. It may prove useful to OIE Reference Laboratories involved in preparing such materials.

The Commission also noted a draft revision of the WHO Recommendations for the Preparation, Characterization and Establishment of International and other Biological Reference Materials. This is in harmony with the existing OIE Guidelines for Preparation of International Reference Sera, but provides considerably more technical detail.

10.9. Information on glanders

Following a recent outbreak of glanders, reported to the OIE by United Arab Emirates, Dr U Wernery from the Central Veterinary Laboratory in Dubai had provided technical information to the Commission on the laboratory diagnostic procedures used. He was liaising with other veterinary laboratories around the world in order to evaluate the diagnostic tests using known positive samples collected during the outbreak.

10.10. OIE/FAO Avian Influenza Network

The Commission participated by teleconference with Dr I. Capua from the OIE Reference Laboratory for Avian Influenza in Padua, Italy, to discuss the formation and terms of reference for a proposed OIE/FAO Avian Influenza Network. The structure and membership in the network were reviewed. A Steering Committee will be chaired by the President of the Commission. The main activities will be led by a Scientific Committee of experts chaired by Dr Capua, supported by a wider team of scientific collaborators. The Commission commented that this network is an important part of the global response to threats of avian influenza, and emphasised the importance of co-ordinating with WHO, as already decided.

10.11 Joint FAO/IAEA Consultants Meeting on Early Warning Devices and Tools, 29 November – 3 December 2004, Vienna, Austria

The President of the Commission had been represented at the above meeting by Dr Kath Webster, head of the Biotechnology Dept at the Veterinary Laboratories Agency, Weybridge, UK. The Commission reviewed her mission report, and took note of the recommendations concerning the development of appropriate diagnostic technology for local needs, but which is capable of validation to international guidelines, the provision of international reference standards, and the development of education and communication tools.

10.12 Mission report: OIE Technical Assistance Mission, 13-17 December 2004, for the People's Republic of China (Beijing) Olympics

Dr Pearson reported on this mission in which he had participated along with 3 other colleagues. The recommendations pertinent to the BSC were that for the People's Republic of China to undertake surveillance for equine diseases: 1) the tests used should be those prescribed by the OIE, 2) the test methods outlined in the OIE *Terrestrial Manual* should be followed, 3) standardised reagents should be used and reagents should be obtained from or exchanged with OIE Reference Laboratories or recognised international laboratories, 4) standardisation of testing by exchange of unknown samples, with the above laboratories, should be considered and 5) the tests described in the OIE *Terrestrial Manual* to confirm questionable results should be put in place.

10.13. WTO Panel letter

The Commission had received a request from the WTO for references defining certain scientific terms. Answers were provided by the library of one of the OIE Reference Laboratories.

10.14. OIE/FAO International Scientific Conference on Avian Influenza, OIE Headquarters, Paris, 7–8 April 2005

The Commission noted the programme for the International Scientific Conference on Avian Influenza and recommended that Prof. Edwards, President of the Commission, give a presentation at the Conference on the proposed new *Terrestrial Manual* chapter on avian influenza.

10.15. Dates of next Biological Standards Commission meeting

The next meetings of the Biologicals Standards Commission will be held from 21 to 23 September 2005 and from 25 to 27 January 2006.

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.../Appendices

Appendix I

MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION

Paris, 26–28 January 2005

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Agenda

1. OIE Reference Laboratories
2. International Standardisation of Diagnostic Tests and Vaccines
3. List of Prescribed and Alternative Tests
4. Report of the Third Meeting of the Ad hoc Group on Nonstructural Protein Tests for Foot and Mouth Disease Diagnosis
5. Report of the Meeting of the Ad hoc Group on Biosafety/Biocontainment Standard
6. Report of the Meeting of the Ad hoc Group on Antimicrobial Resistance
7. *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*
8. Specific procedures for OIE to validate and approve diagnostic tests
9. Liaison with other Commissions
10. Any Other Business

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MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION
Paris, 26–28 January 2005

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GUIDELINES FOR APPLICANTS FOR TWINNING WITH AN OIE REFERENCE LABORATORY

1. Name and address of the OIE Reference Laboratory that agrees to participate in the twinning procedure (Note: a letter from the Director of the Institute confirming the laboratory's willingness to participate must be included with the application).

2. Name and address of proposed 'twinned' laboratory (telephone and fax numbers, e-mail address, Web site where appropriate).

3. Name of Laboratory Director.

4. Name of disease for which capacity building is required.

5. Name of proposed expert (a brief and informal curriculum vitae should be included). It is not expected that he/she is already a recognised expert in the disease, but he/she should demonstrate the capacity to become so through an appropriate training and personal development programme. Evidence of aptitude and commitment should be provided.

For each of the following, provide information on the existing capacity of the laboratory (if none, say so):

6. Experience in diagnostic testing for the disease (approximate number of tests performed annually for each technique).

7. Other activities related to the disease (such as agent characterisation, molecular techniques, application of monoclonal antibodies).

8. Experience in standardisation and validation of diagnostic tests.

9. Reagent production capability (provide details of current stock of reagents for the disease).

10. Capability for timely international shipment in accordance with the requirements for postage and packaging of biological materials described in chapter 1.4.6. of the OIE *Terrestrial Animal Health Code.*

11. Current and completed research and methods development projects on the disease, including a list of relevant publications.

12. Identify development needs and how these will enable the laboratory in the future to fulfil the requirements of an OIE Reference Laboratory. Provide a detailed **work plan** with timescales on how you intend to meet these needs.

Appendix IV

73 SG/12 CS2B/AHG 1

Original: English
September 2004

REPORT OF THE THIRD MEETING OF THE OIE AD HOC GROUP ON EVALUATION OF NONSTRUCTURAL PROTEIN TESTS FOR FOOT AND MOUTH DISEASE DIAGNOSIS

Paris, 6–8 September 2004

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The third meeting of the OIE Ad hoc Group on Evaluation of Nonstructural Protein (NSP) Tests for Foot and Mouth Disease (FMD) Diagnosis was held at OIE Headquarters in Paris from 6 to 8 September 2004.

Dr Alejandro Schudel, Head of the OIE Scientific and Technical Department welcomed the members on behalf of the Director General of the OIE and explained the importance of the application of NSP tests by OIE Member Countries carrying out surveillance for FMD.

The meeting was chaired by Dr Peter Wright, who also acted as rapporteur. The Agenda and the list of participants are presented as Appendices I and II respectively.

1. Background

1.1. First meeting

The Ad hoc Group first met at OIE Headquarters in Paris from 2 to 4 October 2002. At this meeting, the Group conducted a review of current nonstructural proteins enzyme immunoassays and examined available validation data. Diagnostic performance estimates were based on relatively few experimental animals and were found to vary widely amongst these test methods. The disparity in results underscored the need to establish one test method as a fully validated index method. This method would then be used to develop and characterize reference standard sera for the calibration of all other assays.

The indirect ELISA (iELISA) from Panaftosa was selected as the best candidate for the index method. This iELISA, along with the EITB Western Blot technique, had been described in the Foot and Mouth Disease Chapter of the OIE *Manual* (2000 editon).

In addition, a need was identified to develop panels of defined bovine sera that could be used to evaluate and compare the performance characteristics of the various test methods.

Standardization and validation of an NSP system for cattle was considered to be the top priority. Once complete a similar exercise for sheep and then by pigs would then follow.

At the end of the first meeting the Group agreed to work on the completion of a validation dossier for the iELISA (above) and to begin the selection and characterisation of candidate sera for the development of reference standard sera and evaluation panels.

1.2. Second meeting

The Ad hoc Group met for the second time at OIE Headquarters in Paris from 17 to 19 September 2003. A preliminary draft of the validation dossier was examined. Data on analytical and diagnostic performance characteristics were examined and tabulated. The iELISA and EITB were reviewed for technical detail and upgrades with respect to incorporation of new reference standard reagents and internal quality control processes. Revised descriptions of these methods were incorporated into the 2004 edition of the *Terrestrial Manual*.

Dose-response curves of candidate sera were examined and dilution ranges were selected for the strong and weak positive reference standards. Final preparation and testing of strong and weak positive and negative bovine reference standard sera was then to be undertaken.

Initial candidate sera were identified for the evaluation panels. Sera have been obtained from experimental studies in cattle and include non-vaccinated, infected animals, as well as, vaccinated animals that had been subsequently challenged. These sera were to be characterised in the index test and stored for future reference and comparisons. Similar types of sera from sheep and pigs were being sought. Additional sera from all species will be added to the bank as they become available.

The Group felt that sufficient data had now been compiled to begin development of specific application, sampling and interpretation strategies, especially with respect to declaration of freedom.

1.3. Third and current meeting

The Ad hoc Group met recently for the third time. The purpose of this meeting was; a) to assess the NSP validation dossier against the requirements of the new, prototype OIE validation and certification template, b) to review progress on the development and production of reference standard sera and evaluation panels, c) to review additional performance data derived from a recently held NSP ELISA workshop held in Brescia, and d) to review *Terrestrial Animal Health Code* Appendix 3.8.6 relative to the application of NSP tests in FMD surveillance.

2. Validation dossier

2.1. OIE validation and certification template

In May 2003, the OIE adopted a formal process for the validation and certification of diagnostic assays for infectious animal diseases. A prototype template for this process has been developed in collaboration with the Joint FAO/IAEA Division of IAEA in Vienna. The Biological Standards Commission has informally requested that this Group use the prototype template as a pilot using the current NSP index method under evaluation. The Group agreed to comply with their request. Most of the data for the prototype template had already been compiled for cattle and a few key points are still required for further elaboration especially in sheep and pigs.

An amended template is presented as Appendix III.

2.2. Fitness for purpose

One of the principle cornerstones of the proposed validation and certification process is the evaluation of the test method with respect to fitness for purpose. Six general applications are recognized and include; 1) declaration of population freedom, 2) declaration of individual animal freedom, 3) eradication and control, 4) investigation of clinical signs, 5) prevalence estimates for risk analysis, and 6) monitoring of immune status.

Based on evaluation of the data, the Group agrees that the index method, as a screening test, is fit for the following applications; i) declaration of population freedom, ii) eradication and control, and iii) prevalence estimates for risk analysis. Further discussion related to the fitness of the index iELISA for these particular applications may be found Section 4 of this report.

2.3. Analytical characteristics – Calibration

The dose-response characteristics of the index iELISA have been delineated. Three bovine reference standard sera representing a strong and a weak positive serum lying on the linear portion of the dose-response curve and a negative serum have been produced with accompanying data sheets by Panaftosa. These sera will be proposed as official OIE Reference Standard Sera for NSP test methods. They may be used for the analytical calibration of other NSP test methods and for the production and calibration of secondary reference standard sera.

Selection of candidate reference sera for sheep and pigs is making good progress.

2.4. Analytical characteristics – Repeatability

In the original index method protocol, data were expressed as ratios of test sample OD's to cut-off control serum OD (T/C ratios). This requires the establishment of cut-off serum with very low but defined positive activity. On the other hand, OIE guidelines recommend the use of the strong positive control, as defined by the strong positive reference serum above, and expression of results as percent positivity (PP) relative to this control. Both methods of data transformation have been tested in the iELISA and in both cases, the assay has demonstrated acceptable repeatability in the testing of serum samples representing a broad range of antibody activity.

2.5. Diagnostic characteristics – Threshold

As mentioned in section 2.4 above, both T/C ratios and PP may be used as methods for data transformation. In either case, positive-negative thresholds will have to be determined based on the target population, vaccination status and specified application of the test. The validation data presented in this dossier is based on thresholds determined by Panaftosa in the context of testing in vaccinated and non-vaccinated populations in South America.

2.6. Reproducibility

Reproducibility is currently being assessed using a panel of 11 sera representing the full range of expected reactivity. The panel was distributed to 9 South American laboratories using Panaftosa iELISA kits. Not all labs were using the same serial release or batch of kits. Preliminary analysis of the data would suggest that acceptable reproducibility has been demonstrated.

2.7 Evaluation panels

Establishment of reference material collections is recognized as a priority by the OIE. Evaluation panels comprised of fully characterised reference sera serve several functions. Firstly, they may be used to as a starting point for the analytical assessment of a new test or modifications to an existing test. Secondly, they may used in harmonization exercises to assess the diagnostic performance characteristics of multiple tests. And thirdly, they may be used to assess the serial production of reagent or kit batches.

Panels of 30-40 bovine sera that represent a full range of expected activity are being established in at least two OIE Reference Laboratories. It is recognized that these sera will be exhausted eventually and that new sera will need to be incorporated on a continuous basis as they become available. This Group encourages other (reference) laboratories to contribute to these collections as material becomes available. As these panels will be rather limited in quantity, the Group also recommends that where possible, the responsible reference laboratory undertake testing for the applications stated above.

Plans are underway to create similar reference material collections for sheep and pigs.

3. NSP ELISA Workshop – Brescia

A workshop was held in Brescia, Italy (3-15 May 2004) under the auspices of FAO-EUFMD, EC, FP6-FMD-ImproCon and Panaftosa. The purpose of the workshop was to compare the diagnostic performance characteristics of existing immunoassays for the detection of anti-NSP antibodies to that of the OIE index method (Panaftosa iELISA). The organisers graciously shared with the Ad hoc Group, a preliminary report of the results.

The comparison included following test methods; 1) Cedi Test FMDV-NS, 2) Bommeli Chekit FMD-3ABC ELISA, 3) UBI FMD NS ELISA, 4) SVANOVIR FMDV 3ABC-Ab ELISA, 5) Brescia 3ABC Trapping ELISA, and 6) Panaftosa 3ABC iELISA.

Samples were assembled from various sources and included non-vaccinated and vaccinated negative reference animals, infected and vaccinated + infected positive reference animals and field sera of unconfirmed infection status collected during outbreaks. Sera from three species were tested; cattle (2,415), sheep (693), pigs (721).

Although analysis of the data is still ongoing at the time of writing of this report, data on the diagnostic specificity and sensitivity in cattle for the index iELISA has confirmed diagnostic performance data from South America and validates its choice as the OIE index method.

The Group looks forward to seeing the final report and with the permission of the workshop organisers, will add this valuable data on the index iELISA to the validation dossier.

4. *Terrestrial Animal Health Code* Appendix 3.8.7

Considerable discussion took place relative to application of both SP and NSP tests in either vaccinated or non-vaccinated populations. Based on diagnostic specificity and diagnostic sensitivity data, the index iELISA is well suited as a screening test in combination with suitable confirmatory tests, such as the EITB, for several applications. With proper sampling strategies, these include; a) declaration of population freedom, b) surveillance programs, c) prevalence surveys, and d) outbreak management, especially recovery.

Appendix 3.8.7 had been extensively reviewed by the Ad hoc Group on Epidemiology in June, 2004. It deals specifically with guidelines for surveillance in support of regaining FMD-free recognition in a country or zone. The Epidemiology Group had incorporated a number of revisions that may be found in their meeting report. The NSP Group was asked their comments in general but more specifically on Article 3.8.7.6 – *The use and interpretation of serological tests*. The following additions/changes to this Article were suggested.

> *Serological testing is a suitable tool for FMD surveillance. The choice of a serosurveillance system will depend on, amongst other things, the vaccination status of the country. A country, which is free from FMD without vaccination, may choose serosurveillance of high-risk subpopulations (e.g. based on geographical risk for exposure to FMDV). SP tests may be used in such situations for screening sera for evidence of FMDV infection/circulation if a particular virus of serious threat has been identified and is well characterised. In other cases, NSP testing is recommended in order to cover a broader range of strains and even serotypes. In both cases, serological testing can provide additional support to clinical surveillance. Regardless of whether SP or NSP tests are used in countries that do not vaccinate, a diagnostic follow-up protocol should be in place to resolve any preliminary (presumptive) positive serological test results.*
>
> *In areas where animals have been vaccinated, SP antibody tests may be used to monitor the serological response to the vaccination. However, NSP antibody tests should be used to monitor for FMDV infection/circulation. NSP-ELISAs may be used for screening sera for evidence of infection/circulation irrespective of the vaccination status of the animal. All herds with seropositive reactors should be investigated. Epidemiological and supplementary laboratory investigation results should document the status of FMDV infection/circulation for each positive herd. Tests used for*

confirmation should be of high diagnostic specificity to eliminate as many false positive screening test reactors as possible. Wherever feasible, the diagnostic sensitivity of the confirmatory test should approach that of the screening test. The EITB or another OIE-accepted test should be used for confirmation.

Information should be provided on the protocols, reagents, performance characteristics and validation of all tests used.

5. Future work

5.1 Conventional vs. high potency vaccines

Most of the available data with respect to induction of carrier states and seroconversion is based on conventional doses of vaccine. Work still needs to be done to determine whether or not the use of high potency vaccines will alter carrier states and DSn estimates in vaccinated animals.

5.2. Reference standard sera

The characterisation and development of reference standard sera for sheep and pigs will be initiated.

5.3. Evaluation panels

The development of evaluation panels should continue for all species. The composition, application and interpretation of these panels needs to be developed into guidelines with respect to analytical assessment, harmonization exercises and the serial release of reagent or kit batches

5.4. Validation and certification dossiers

Since most of the available data have been validated for cattle, it would be desirable to compile and evaluate data with respect to expanding the current dossier to include sheep and pigs.

5.5 Next meeting

It is proposed that the Ad hoc Group meet in one years' time to review progress on the above and report to the Biological Standards Commission.

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…/Appendices

Appendix I

REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON EVALUATION OF NON STRUCTURAL PROTEINS TESTS FOR FOOT AND MOUTH DISEASE DIAGNOSIS

Paris, 6 – 8 September 2004

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Agenda

1. Background

1.1. First meeting
1.2. Second meeting
1.3. Third and current meeting

2. Validation dossier

2.1. OIE validation and certification template
2.2. Fitness for purpose
2.3. Analytical characteristics – Calibration
2.4. Analytical characteristics – Repeatability
2.5. Diagnostic characteristics – Threshold
2.6. Reproducibility
2.7 Evaluation panels

3. NSP ELISA Workshop – Brescia

4. *Terrestrial Animal Health Code* Appendix 3.8.7

5. Future work

5.1 Conventional vs. high potency vaccines
5.2. Reference standard sera
5.3. Evaluation panels
5.4. Validation and certification dossiers
5.5 Next meeting

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Appendix II

REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON EVALUATION OF NON STRUCTURAL PROTEINS TESTS FOR FOOT AND MOUTH DISEASE DIAGNOSIS

Paris, 6 – 8 September 2004

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List of Participants

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Appendix III

Validation Template Check List

	ELEMENT	DOSSIER STATUS	COMMENTS
1	Background Information		
1.1	Test method	Complete	Indirect ELISA for the detection of bovine antibody to the 3ABC Polyprotein of FMDV
1.2	Intended purpose(s) of test	Complete	Population freedom (declaration) Eradication/control Prevalence estimate (risk analysis)
1.3	Applicant	Complete	Panaftosa
1.4	Scientific contact	Complete	Ingrid Bergmann
1.5	Accreditation or certification status of laboratory	Complete	OIE Ref Lab
1.6	Intellectual property	Complete	Public domain
2	Test Method		
2.1	Protocol	Complete	ELISA and EITB protocols described in *Manual*
2.2	Kit configuration (if Commercial)	Complete	Kits provided to South American labs
3	Validation – Stage I		
3.1	Calibration	Complete	New calibration reagents developed
3.2	Repeatability	Complete	CV's established for raw and transformed data
3.3	Analytical specificity	Complete	Antisera to various viruses tested
3.4	Analytical sensitivity	Complete	Based on earliest detection and endpoint titers
4	Validation - Stage II		
4.1	Reference Animals		
4.1.1	Negative reference animals	Complete	Defined and grouped
4.1.2	Positive reference animals	Complete	Defined and grouped
4.1.3	Experimental animals	Complete	Defined and grouped
4.2	Threshold determination	Complete	Established for South America
4.3	Performance Estimates		
4.3.1	Dx Se and Sp estimates – with defined reference animals	Complete	Based on South American and European sera
4.3.2	Dx Se and Sp estimates – without defined reference animals	Not applicable	
4.3.3	Agreement between tests	Complete	Assessed relative to OP, EITB, AGID and other ELISA's
5	Validation – Stage III		
5.1	Laboratory selection	Complete	Tech transfer to South American labs
5.2	Evaluation panel	In progress	Bovine panels being established in two OIE Ref Laboratories
5.3	Reproducibility	Complete	Assessed on kits distributed to South American labs
6	Validation – Stage IV		
6.1	Laboratories	Complete	Regional – South American labs
6.2	Test applications	Complete	Population freedom (declaration) Eradication/control Prevalence estimate (risk analysis)
6.3	International reference reagents	Pending	New reagents awaiting OIE approval
6.4	Inter-laboratory testing programs	Complete	South America presently
6.5	International recognition	Pending	OIE certification pending

Appendix V

73 SG/12 CS2B/AHG 2

Original : anglais
October 2004

REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON BIOSAFETY/BIOCONTAINMENT STANDARD

San Antonio, Texas, USA, 18 October 2004

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A meeting of the OIE Ad hoc Group on Biosafety/Biocontainment Standard was held at the Crowne Plaza Hotel, San Antonio, Texas on 18 October 2004. The meeting was chaired by Dr Beverly Schmitt, Vice-President of the OE Biological Standards Commission, who also acted as rapporteur. The Agenda and List of Participants are given at Appendices I and II, respectively.

Members of the Ad hoc Group in attendance were initially given the Terms of Reference for this project (Appendix III) and the current OIE reference materials on biosafety/biocontainment by Dr Schmitt. The ensuing discussion addressed the following issues:

- countries need to assess their own disease risk when considering biocontainment levels;
- current OIE biosafety chapter deals primarily with human pathogens, veterinary pathogens have additional requirements; emphasize concept of biocontainment;
- need to explain in new standard why certain requirements are necessary;
- isolation of agents (prevent cross-contamination, worker and environment protection);
- initial classification of a specimen and its hazard classification is based upon a clinical diagnosis;
- biosafety, biocontainment and biosecurity need to be defined;
- should new biocontainment standard be part of Manual or stand-alone document?

The following are decisions and action items from the meeting:

1. The new standard should be a stand-alone OIE document and include both the revised biosafety chapter and biocontainment standard. The Ad hoc Group and other international experts will use P. Mani's Web site to access and comment on drafts of the document.

2. The new biocontainment standard needs to include standards for risk group 2 in order to address the needs of developing countries.

3. The standard should include information on general operation protocols.

4. Suggested title of new standard: “Biosafety Practices and Protocols for Facilities Using Pathogens of Veterinary Concern”.

5. P. LeBlanc-Smith and P. Cairns will be co-authors of new Manual chapter on biosafety. Peter LeBlanc-Smith will draft some language to address veterinary pathogen issues in current Manual biosafety chapter.

6. B. Schmitt will contact OIE in regards to when the International Committee is meeting in May 2005 and what the expectations are. The International group on veterinary biosafety meets in Sweden May 10 to 12, 2005.

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…/Appendices

Appendix I

MEETING OF THE OIE AD HOC GROUP ON BIOSAFETY/BIOCONTAINMENT STANDARD

San Antonio, Texas, USA, 18 October 2004

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Agenda

1. Welcome
2. Terms of reference for Ad hoc Group
3. Existing standards
   a. OIE *Terrestrial Animal Health Code* Chapter
   b. OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* Chapter
   c. WHO Laboratory Biosafety Manual
   d. CDC/NIH Biosafety in Microbiological and Biomedical Laboratories
   e. Other?
4. Discussion on composition of OIE Biocontainment/Biosafety Standard
   a. What is the audience for this Standard?
   b. Why is this Standard needed?
   c. What is the goal of the Standard?
   d. Relation of this Standard to the OIE *Terrestrial Manual* and *Terrestrial Code*
   e. Will this be a complete 'stand alone' publication?
   f. How detailed?
   g. Should information in existing Standards be repeated in the new Standard?
   h.
   i. Author for the OIE *Terrestrial Manual* chapter
5. Group assignments
6. Adjourn

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Appendix II

MEETING OF THE OIE AD HOC GROUP ON BIOSAFETY/BIOCONTAINMENT STANDARD

San Antonio, Texas, USA, 18 October 2004

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List of Participants

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Appendix III

Terms of Reference for the OIE Ad hoc Group on Biocontainment/Biosafety Standard

- To develop an international standard for the design, construction, and operation of veterinary laboratories and animal facilities dealing with biological agents (and toxins);

- To take account of existing standards and guidelines for both animal pathogen containment and human biosafety;

- To report to the OIE Biological Standards Commission.

It is hoped that the first draft of this standard would be completed by May 2005.

73 SG/12 CS2B/AHG 3

Original: English
November 2004

REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 15–17 November 2004

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A meeting of the OIE Ad hoc Group on Antimicrobial Resistance was held at the OIE Headquarters in Paris from 15 to 17 November 2004. The meeting was chaired by Dr Herbert Schneider; Dr Christopher Teale from the OIE Reference Laboratory for antimicrobial resistance acted as rapporteur. The Agenda and List of Participants are given at Appendices I and II, respectively.

1. Welcome and introductory remarks

Dr Alejandro Schudel, Head, OIE Scientific and Technical Department, welcomed the participants on behalf of the Director General of the OIE and outlined the proposed agenda for the meeting. He indicated that the membership of the Ad hoc Group has changed to reflect the current areas of interest. It is envisaged that this Group will meet annually or biannually, as appropriate, over the next few years.

2. Review of Member Country comments on Appendix 3.9.4 of the OIE *Terrestrial Animal Health Code* on Risk analysis for antimicrobial resistance

All comments received from OIE Member Countries relating to Appendix 3.9.4 of the *Terrestrial Animal Health Code* (*Terrestrial Code*) on Risk analysis for antimicrobial resistance were considered by the Ad hoc Group. Although all comments were taken into account, not all could be accommodated in the final review. Three general points were raised by the Ad hoc Group during the review procedure:

- Risk communication and risk management are covered in Section 1.3 of the *Terrestrial Code* – there is a need for a general paragraph in Chapter 1.3.2 to cover specific aspects relating to antimicrobial resistance (see Appendix III for the proposed draft text).

- Aquaculture was not covered in the *Terrestrial Code* and the Group recommended that the issue of antimicrobial resistance pertaining to aquaculture be referred to the Aquatic Animal Health Standards Commission (Aquatic Animals Commission) for further deliberations.

- Because the use of antimicrobials in aquaculture farming systems is of great importance, the Group requests the Aquatic Animals Commission to address this issue as a matter of high priority.

The Group also noted that Appendix 3.9.4 deals with resistance arising from the **use** of antimicrobials in animals only, whereas resistance from other sources is not addressed.

The Group believed that the comments from the USA in respect to risk management options were valid regarding the possibility of trade interference for animals and animal products, and that it would be appropriate for the OIE Terrestrial Animal Health Standards Commission to consider this aspect.

The reviewed draft of Appendix 3.9.4 is given at Appendix IV, with the modifications recommended by the Ad hoc Group clearly marked.

3. Terms of reference for the establishment of list of critically important antimicrobials for veterinary medicine/animal husbandry

One conclusion of the Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options, held in Oslo, Norway from 15 to 18 March 2004, was the need to identify antimicrobials that are critically important in veterinary medicine.

An essential preliminary requirement is to define exactly which compounds are covered by the term 'antimicrobial' and the relation to other potentially important compounds, such as anti-coccidials.

A draft paper discussing the terms of reference for an Expert Group charged with establishing the list of critically important antimicrobials for veterinary medicine/animal husbandry was tabled by Dr Gerard Moulin, an expert from the OIE Collaborating Centre for Veterinary Medicinal Products, Fougères, France, and can be found at Appendix V. The draft paper incorporated the relevant comments raised in the FDA[1] Guidance for Industry No. 152, VICH[2] Guidance on Pre-approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance, and the Australian Government's Joint Expert Committee on Antimicrobial Resistance (JETACAR) document on Current Antibiotic Use Patterns.

The functions of the list need to be defined to allow practical implementation of the OIE risk assessment guidelines. The establishment of the list of antimicrobials that are critically important for veterinary medicine/animal husbandry should be done in co-ordination with the establishment of a list of antimicrobials that are critically important for human medicine.

Consideration should be given to the availability of sources of reliable information for developing countries that can be used to assist in the risk assessment of certain antimicrobials for use under local conditions in livestock.

A universal, global list might not be achievable. There are also uncertainties relating to the prediction of emergent diseases (and resistances) and the proposed list should be revised on a regular basis.

In all circumstances, the variation in global and regional animal husbandry methods should be borne in mind when establishing the proposed list.

There may be fundamental differences between the criteria used to appraise the proposed human and animal lists (economic and welfare considerations paramount in animals).

The Group notes that there are fundamental differences in respect of antimicrobial use in food-producing and companion animals.

The Group also recommends that the OIE participates in the forthcoming WHO 'critical list meeting' to be held in Canberra, Australia.

The following are the recommended terms of reference for the proposed OIE Expert Group on Veterinary Critically Important Antimicrobials (VCIA):

This Expert Group should consider recent recommendations and texts (including FAO/OIE/WHO workshops) relating to the establishment of a list of VCIA.

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1 FDA: US Food and Drug Administration

2 VICH: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

Mission

To propose a methodology for establishing the list of VCIA.

- In order to do so, the Expert Group should first define the criteria that should be taken into account, if possible in coordination with WHO.

- The Expert Group should examine the different criteria that could apply to the veterinary list.

Procedure

Considering the current definition of antimicrobials given at Agenda Item 5 of this report, the Expert Group should:

- Identify relevant species (food-producing animals, companion animals and aquatic species) in which antimicrobials are used.
- Consult appropriate bodies (OIE Member Countries, veterinarians, industry, regulatory authorities) in establishing the list. This consultation phase is considered essential.

The Expert Group should also consider and take into account:

- The major diseases of animals, including aquatic animals,
- The approved and marketed products and their condition of use (species, route of administration, diseases),
- The possible alternative antimicrobial options and management strategies,
- Cross and co-resistance between antimicrobials,
- The economic costs (diseases, antimicrobials concerned),
- Animal welfare aspects,
- The situation in different countries.

Outcome

- Establish criteria for the establishment of a list of VCIA.
- Consider the feasibility of a global list versus local (national) and regional lists.
- Consider, in co-operation with WHO, classification systems for antimicrobials (classes, chemical form and international units).
- Provide a list of VCIA.

The following items should be addressed in preparation for the January 2005 meeting of the Ad hoc Group on Antimicrobial Resistance:

- Provide a framework for completion by the Expert Group.
- Define purposes for which the list may be suitable (risk assessment only or other purposes).
- Produce questionnaire for OIE Member Countries (may be done in January).

4. Codex Alimentarius Commission's Guidelines for Prudent Use of Antimicrobials

Dr Patrick Dehaumont, OIE Expert from the OIE Collaborating Centre for Veterinary Medicinal Products, Fougères, France, presented this agenda item. Appendix 3.9.3 of the *Terrestrial Code* on Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine was adopted by the OIE International Committee at the General Session in 2003. The Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) also produced a Draft Code of Practice on the Use of Antimicrobial Drugs in March 2003, with input from many delegations. The documents are similar in content and overall scheme, but care is needed to avoid redundancies and discrepancies between the documents. It is proposed that the Codex adopts the OIE Guidelines at the earliest opportunity, and also that a joint Codex/OIE task force be

established, if possible (a recommendation from the Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment, held in Geneva, Switzerland, in December 2003). The Codex is currently consulting member countries in order to define what responsibilities should be given to Codex Alimentarius and which methodology should be put in place as far as antimicrobial resistance is concerned, and will discuss the results of the consultation at its next Executive Meeting.

Based on the information presented, the Ad hoc Group recommends that it proceeds to review Appendix 3.9.3 of the *Terrestrial Code* to take into account recent developments in the Codex draft.

The OIE has responded to the Codex expressing its willingness to co-operate in the development of harmonised and common approaches, and the OIE Ad hoc Group on Antimicrobial Resistance will examine the Codex and OIE documents at its next meeting in January 2005. A key requirement was the need for a common definition of 'antimicrobial' (addressed at item 5). Discussion at the Ad hoc Group on Antimicrobial Resistance meeting in January will allow the documents developed to be considered later in 2005 at the relevant Codex and OIE meetings.

The Ad hoc Group considers it necessary to address at forthcoming meetings the practical implementation of the OIE Guidelines on antimicrobial resistance.

5. Ad hoc Group's definition of 'antimicrobial agent'[3]

This Group recognises the urgent need for a definition of the term 'antimicrobial' and proposes the following term to the OIE Terrestrial Animal Health Standards Commission for adoption:

Antimicrobial agents in veterinary medicine refers to naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (*kill or inhibit the growth of micro-organisms*).

6. Date of next meeting

The next meeting of the Ad hoc Group on Antimicrobial Resistance shall be from 26 to 28 January 2005 at the OIE Headquarters in Paris. Its purpose will be to focus on VCIA.

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…/Appendices

3 This proposal will be submitted for approval to the OIE Biological Standards Commission.

Appendix I

MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 15–17 November 2004

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Agenda

1. Welcome and introductory remarks

2. Review of Member Country comments on Appendix 3.9.4 of the OIE *Terrestrial Animal Health Code* on Risk analysis for antimicrobial resistance

3. Terms of reference for the establishment of list of critically important antimicrobials for veterinary medicine/animal husbandry

4. Codex Alimentarius Commission's Guidelines for Prudent Use of Antimicrobials

5. Ad hoc Group's definition of 'antimicrobial agent'

6. Date of next meeting

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Appendix II

MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE
Paris, 15–17 November 2004

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Appendix III

CHAPTER 1.3.2.

GUILELINES FOR IMPORT RISK ANALYSIS

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Article 1.3.2.8.

The relevant recommendations (Articles 1.3.2.7, 1.3.2.5 and 1.3.2.6) in the *Terrestrial Code* apply.

A range of risk management options is available to minimise the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory risk management options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. Risk management decisions need to consider fully the implications of these different options for human health and animal health and welfare and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial diseases of animals will have the additional benefit of reducing the risks linked to antimicrobial resistance, in cases where the bacterial disease under consideration has also developed antimicrobial resistance. Appropriate communication with all stakeholders is essential throughout the risk assessment process.

Appendix IV

APPENDIX 3.9.4.

RISK ~~ANALYSIS~~ ASSESSMENT FOR ANTIMICROBIAL RESISTANCE ARISING FROM THE USE OF ANTIMICROBIALS IN ANIMALS

Article 3.9.4.1.

Guidelines for analysing the risks to animal and public health from antimicrobial resistant bacteria of animal origin

1) Introduction

The use of antimicrobials for therapy, prophylaxis and growth promotion in animals can reduce their efficacy in animal and human medicine, through the development of antimicrobial resistant strains of pathogenic bacteria. This risk may be represented by the loss of therapeutic efficacy of one or several antimicrobial drugs and includes the emergence of multi-resistant bacteria.

2) Objective

The principal aim of risk analysis for antimicrobial resistance in bacteria from animals is to provide Member Countries with a transparent, objective and scientifically defensible method of assessing and managing the human and animal health risks associated with the development of resistance arising from the use of antimicrobials in animals.

3) The risk analysis process

The principles of risk analysis are described in Section 1.3. of the *Terrestrial Code*.

A qualitative risk assessment should always be undertaken. Its outcome will determine whether progression to a quantitative risk assessment is feasible and/or necessary.

4) Hazard identification

For the purposes of this Appendix, the hazard is the resistance determinant that emerges as a result of the use of a specific antimicrobial in animals. This definition reflects the development of resistance in a species of pathogenic bacteria, as well as the development of a resistance determinant that may be passed from one species of bacteria to another. The conditions under which the hazard might produce adverse consequences include any ~~feasible~~ scenarios through which humans or animals could become exposed to a pathogen which contains that resistance determinant, fall ill and then be treated with an antimicrobial that is no longer effective because of the resistance.

5) Risk assessment

The assessment of the risk to human and animal health from antimicrobial-resistant bacteria resulting from the use of antimicrobials in animals should examine:

a) the likelihood of emergence of resistant bacteria arising from the use of antimicrobial(s), or more particularly, production of the resistant determinants if transmission is possible between bacteria;

Appendix IV (contd)

b) consideration of all pathways and their importance, by which humans could be exposed to these resistant bacteria or resistance determinants, together with the possible ~~dose of bacteria in the~~ degree of exposure;

c) the consequences of exposure and the estimated probability of its occurrence.

Article 3.9.4.2.

Analysis of risks to human health

1) Definition of the risk

The infection of humans with bacteria that have acquired resistance to a specific antimicrobial used in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the human infection.

2) Hazard identification

- Bacteria that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial(s) in animals.

- Bacteria having obtained a resistance determinant(s) from other bacteria which have acquired resistance arising from the use of an antimicrobial(s) in animals.

The identification of the hazard must include consideration of the class or subclass of the antimicrobial(s). This definition should be read in conjunction with 3.9.4.1.4.

3) Release assessment

A release assessment describes the biological pathways necessary for the use of a specific antimicrobial in animals to lead to the release of resistant bacteria or resistance determinants into a particular environment, and estimating either qualitatively or quantitatively the probability of that complete process occurring. The release assessment describes the probability of the release of each of the potential hazards under each specified set of conditions with respect to amounts and timing, and how these might change as a result of various actions, events or measures.

The following factors should be considered in the release assessment:

- species of animal treated with the antimicrobial(s) in question
- number of animals treated, geographical distribution of those animals
- amounts used and duration of treatment
- variation in methods and routes of administration of the antimicrobial(s)
- the pharmacodynamics/pharmacokinetics of the antimicrobial(s)
- bacteria developing resistance as a result of the antimicrobial(s) use
- mechanism of direct or indirect transfer of resistance
- cross-resistance and/or co-resistance with other antimicrobials
- surveillance of animals, ~~animal~~ products of animal origin and animal waste products for the existence of resistant bacteria.

4) Exposure assessment

An exposure assessment describes the biological pathways necessary for exposure of humans to the resistant bacteria or resistance determinants released from a given antimicrobial use in animals, and estimating the probability of the exposures occurring. The probability of exposure to the identified hazards is estimated for specified exposure conditions with respect to amounts, timing, frequency, duration of exposure, routes of exposure and the number, species and other characteristics of the human populations exposed.

The following factors should be considered in the exposure assessment:

- human demographics and food consumption patterns, including traditions and cultural practices
- prevalence of resistant bacteria in food
- ~~animal environment contaminated~~ environmental contamination with resistant bacteria
- prevalence of animal feed contaminated with resistant bacteria
- cycling of resistant bacteria between humans, animals and the environment
- steps of microbial decontamination of food
- microbial load in contaminated food at the point of consumption
- survival capacity and redistribution of resistant bacteria during the food production process (including slaughtering, processing, storage, transportation and retailing)
- disposal practices for waste products and the opportunity for human exposure to resistant bacteria or resistance determinants in those waste products
- point of consumption of food (professional catering, home cooking)
- variation in consumption and food-handling methods of exposed populations and subgroups of the population
- capacity of resistant bacteria to become established in ~~human intestinal flora~~ humans
- human-to-human transmission of the bacteria under consideration
- capacity of resistant bacteria to transfer resistance to human commensal bacteria and zoonotic agents
- amount and type of antimicrobials used in response to human illness
- dose, route of administration (oral, parenteral) and duration of human treatment
- pharmacokinetics (metabolism, bioavailability, access to intestinal flora).

5) Consequence assessment

A consequence assessment describes the relationship between specified exposures to resistant bacteria or resistance determinants and the consequences of those exposures. A causal process must exist by which exposures produce adverse health or environmental consequences, which may in turn lead to socio-economic consequences. The consequence assessment describes the potential consequences of a given exposure and estimates the probability of them occurring.

Appendix IV (contd)

The following factors should be considered in the consequence assessment:

- dose–response relationships
- variation in disease susceptibility of exposed populations or subgroups of those populations
- variation and frequency of human health effects resulting from loss of efficacy of antimicrobials
- changes in human medicinal practices resulting from reduced confidence in antimicrobials
- changes in food consumption patterns due to loss of confidence in the safety of food products and any associated secondary risks
- associated costs
- interference with ~~a classical~~ first line/choice antimicrobial therapy in humans
- perceived future usefulness of the antimicrobial (time reference)
- prevalence of resistance in human bacterial pathogens under consideration.

6) Risk estimation

A risk estimation integrates the results from the release assessment, exposure assessment and consequence assessment to produce overall estimates of risks associated with the hazards. Thus, risk estimation takes into account the whole of the risk pathway from hazard identification to the unwanted consequences.

The following factors should be considered in the risk estimation:

- number of people falling ill and the proportion of that number affected with resistant strains of bacteria
- increased severity or duration of infectious disease
- number of person/days of illness per year
- deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)
- importance of the pathology caused by the target bacteria
- absence of alternate antimicrobial therapy
- incidence of resistance observed in humans
- ~~some arbitrary scale of~~ consequences to allow weighted summation of different risk impacts (e.g. illness and hospitalisation).

7) Risk management options and risk communication

Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

Article 3.9.4.3.

Analysis of risks to animal health

1) Definition of the risk

The infection of animals with bacteria that have acquired resistance from the use of a specific antimicrobial(s) in animals, and resulting in the loss of benefit of antimicrobial therapy used to manage the animal infection.

2) Hazard identification

- Bacteria that have acquired resistance, (including multiple resistance) arising from the use of an antimicrobial(s) in animals.

- Bacteria having obtained a resistance determinant(s) from ~~another~~ other bacteria which have acquired resistance arising from the use of an antimicrobial(s) in animals.

The identification of the hazard must include considerations of the class or subclass of the antimicrobial(s). This definition should be read in conjunction with point 4 of the Article 3.9.4.1.

3) Release assessment

The following factors should be considered in the release assessment:

- animal species treated
- number of animals treated, sex, age and their geographical distribution
- amounts used and duration of treatment
- variation in methods and routes of administration of the antimicrobial(s)
- the pharmacodynamics/ pharmacokinetics of the antimicrobial(s)
- site and type of infection
- development of resistant bacteria
- mechanisms and pathways of resistance transfer
- cross-resistance and/or co-resistance
- surveillance of animals, ~~animal~~ products of animal origin and animal waste products for the existence of resistant bacteria.

4) Exposure assessment

The following factors should be considered in the exposure assessment:

- prevalence and trends of resistant bacteria in clinically ill and clinically unaffected animals
- prevalence of resistant bacteria in feed /the animal environment

Appendix IV (contd)

- animal-to-animal transmission of the resistant bacteria
- number/percentage of animals treated
- dissemination of resistant bacteria from animals (animal husbandry methods, movement of animals)
- quantity of antimicrobial(s) used in animals
- treatment regimens (dose, route of administration, duration)
- survival capacity of resistant bacteria
- exposure of wild life to resistant bacteria
- disposal practices for waste products and the opportunity for animal exposure to resistant bacteria or resistance determinants in those products
- capacity of resistant bacteria to become established in animal intestinal flora
- exposure to resistance determinants from other sources
- dose, route of administration and duration of treatment
- pharmacokinetics (metabolism, bioavailability, access to intestinal flora)
- cycling of resistant bacteria between humans, animals and the environment.

5) Consequence assessment

The following factors should be considered in the consequence assessment:

- dose–response relationships
- variation in disease susceptibility of exposed populations and subgroups of ~~the~~ those populations
- variation and frequency of animal health effects resulting from loss of efficacy of antimicrobials
- changes in ~~veterinary medicine~~ practices resulting from reduced confidence in antimicrobials
- associated cost
- perceived future usefulness of the drug (time reference).

6) Risk estimation

The following factors should be considered in the risk estimation:

- number of therapeutic failures due to resistant bacteria
- animal welfare
- economic cost

- deaths (total per year; probability per year or lifetime for a random member of the population or a member of a specific more exposed sub-population)

- incidence of resistance observed in animals.

7) Risk management options and risk communication

Risk management options and risk communication have to be continuously monitored and reviewed in order to ensure that the objectives are being achieved.

The relevant recommendations (Articles 1.3.2.7, 1.3.2.5 and 1.3.2.6) in the *Terrestrial Code* apply.

A range of risk management options is available to minimize the emergence and spread of antimicrobial resistance and these include both regulatory and non-regulatory risk management options, such as the development of codes of practice concerning the use of antimicrobials in animal husbandry. Risk management decisions need to consider fully the implications of these different options for human health and animal health and welfare and also take into account economic considerations and any associated environmental issues. Effective control of certain bacterial diseases of animals will have the dual benefit of reducing the risks linked to antimicrobial resistance, in cases where the bacterial disease under consideration has also developed antimicrobial resistance. Appropriate communication with all stakeholders is essential throughout the risk assessment process.

Appendix V

CRITICALLY IMPORTANT ANTIMICROBIALS FOR ANIMALS

(Based on a draft paper by Dr G. Moulin, as modified by the Ad hoc Group.)

Terms of Reference for the Ad hoc Group

Background

The FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance held in Geneva, Switzerland, in December 2003 (Scientific Assessment) and in Oslo, Norway, in March 2004 (Management Options) recommended that the OIE should develop a list of critically important antimicrobials in veterinary medicine. WHO should also develop such a list for critically important antimicrobials in human medicine.

Conclusion No. 5 of the Oslo Workshop is as follows:

> 5. The concept of "critically important" classes of antimicrobials for humans should be pursued by WHO. The Workshop concluded that antimicrobials that are critically important in veterinary medicine should be identified, to complement the identification of such antimicrobials used in human medicine. Criteria for identification of these antimicrobials of critical importance in animals should be established and listed by OIE. The overlap of critical lists for human and veterinary medicine can provide further information, allowing an appropriate balance to be struck between animal health needs and public health considerations.

General considerations

In 2003, the OIE adopted Appendix 3.9.4 of the *Terrestrial Animal Health Code* on Risk analysis for antimicrobial resistance. In this Appendix, the consequence assessment and the risk estimation sections refer to criteria that could be included under the umbrella of 'Critically Important Antimicrobials [CIA]').

In October 2003, the United States FDA published Guidance for Industry No. 152, which is based on the OIE risk analysis and develops a ranking of antimicrobial drugs according to their importance in human medicine.

Other attempts to classify antimicrobials have been done in the past. The Australian JETACAR report has proposed a classification of antimicrobials considered essential in human and animal medicine.

The recent VICH guideline, VICH GL27 (Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance) indicates what are the data to be provided with a Marketing Authorisation dossier. The amount of data to be provided is clearly linked to the perceived importance of the drug (or related drug) to human medicine.

It is quite clear that the establishment of lists of CIA in human and animals will facilitate the practical implementation of the OIE risk analysis concepts.

The following are the recommended terms of reference for the proposed OIE Expert Group on Veterinary Critically Important Antimicrobials (VCIA)

This Expert Group should consider recent recommendations and texts (including FAO/OIE/WHO Workshops) relating to the establishment of a list of VCIA.

Appendix V (contd)

Mission

To propose a methodology for establishing the list of VCIA.

- In order to do so, the Expert Group should first define the criteria that should be taken into account, if possible in coordination with WHO.

- The Expert Group should examine the different criteria that could apply to the veterinary list.

Procedure

Considering the current definition of antimicrobials given by the OIE Ad hoc Group on Antimicrobial Resistance at its meeting of 15–17 November 2004:

- Identify relevant species (food-producing, companion animals and aquatic species) in which antimicrobials are used.

- Consult appropriate bodies (OIE Member Countries, veterinarians, industry, regulatory authorities) in establishing the list. This consultation phase is considered essential.

The Expert Group should also consider and take into account:

- The major diseases of animals, including aquatic animals,

- The approved products and their condition of use (species, route of administration, diseases),

- The possible alternative antimicrobial options and management strategies,

- Cross and co-resistance between antimicrobials,

- The economic costs (diseases, antimicrobials concerned),

- Animal welfare aspects,

- The situation in different countries.

Outcome

- Establish criteria for the establishment of a list of VCIA.

- Consider the feasibility of a global list versus local (national) regional lists.

- Consider, in co-operation with WHO, classification systems for antimicrobials (classes, chemical form and international units).

- Provide a list of VCIA.

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73 SG/12 CS2B/AHG 4

Original: English
January 2005

REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 26–28 January 2005

A meeting of the OIE Ad hoc Group on Antimicrobial Resistance was held at the OIE Headquarters in Paris from 26 to 28 January 2005. The meeting was chaired by Dr Herbert Schneider; Mr Christopher Teale from the OIE Reference Laboratory for Antimicrobial Resistance acted as rapporteur. The Agenda and List of Participants are given at Appendices I and II, respectively.

1. Welcome and introductory remarks

Dr Alejandro Schudel, Head, OIE Scientific and Technical Department, welcomed the participants on behalf of the Director General of the OIE and outlined the proposed agenda for the meeting. He indicated that the membership of the Ad hoc Group has changed to reflect the current areas of interest. It is envisaged that this Group will meet annually or biannually, as appropriate, over the next few years.

2. Revision of Appendix 3.9.3 of the OIE *Terrestrial Animal Health Code* on Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine

Appendix 3.9.3 of the OIE *Terrestrial Animal Health Code* on Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine was revised, taking into account the recommendations of the Codex Alimentarius – ALINORM 05/28/31, Appendix VIII 53 Proposed Draft Code of Practice to Minimize and Contain Antimicrobial Resistance. The revisions made to Appendix 3.9.3 are given at Appendix III of this document.

Codex Alimentarius will discuss the possible formation of a joint Codex/OIE Task Force on Antimicrobial Resistance in February 2005, when the results of a consultation regarding the proposed Task Force would be considered.

3. Critically important antimicrobials for veterinary medicine/animal husbandry: criteria for selection and production of a list of critical veterinary antimicrobials

Dr Jacques Acar will represent the OIE at a forthcoming WHO[1] meeting in Canberra, Australia, at which the critically important antimicrobials for human medicine will be discussed.

A paper was presented by Dr Gérard Moulin proposing criteria for the selection of critically important antimicrobials for veterinary medicine. This was used as the basis for discussion and to produce the paper given at Appendix IV, which establishes outline criteria for the selection of critical veterinary antimicrobials and envisages the consultation with stakeholders that OIE will organise relating to this issue.

[1] WHO: World Health Organization

4. Other matters

Classification of Antimicrobials

At the second Joint FAO[2]/OIE/WHO Expert Workshop on Non-human Antimicrobial Usage and Antimicrobial Resistance, held in Oslo, Norway, it was concluded that data from surveillance of antimicrobial usage are essential for risk assessment and risk management. The establishment of surveillance programmes on antimicrobial usage requires information on the classes and quality of antimicrobials that are available in a country. An internationally agreed nomenclature for antimicrobials available for non-human and human usage (classes, chemical form, and international unit) is essential if data are to be comparable. This nomenclature should be established by a WHO/OIE committee and should relate to more detailed classification systems, such as the Anatomical Therapeutical Chemical (ATC) and Anatomical Therapeutical Chemical Veterinary (ATC-Vet) Classification.

At Appendix V a draft paper on classification was tabled and noted. It is recommended that this be further discussed at appropriate levels within the OIE.

5. Date of next meeting

The next meeting of the OIE Ad hoc Group on Antimicrobial Resistance will be held during or after September 2005, at the OIE Headquarters in Paris.

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[2] FAO: Food and Agriculture Organization of the United Nations

Appendix I

MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 26–28 January 2005

_____

Agenda

1. Welcome and introductory remarks

2. Revision of Appendix 3.9.3 of the OIE *Terrestrial Animal Health Code* on Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine

3. Critically important antimicrobials for veterinary medicine/animal husbandry: criteria for selecting and list of critical veterinary antimicrobials

4. Other matters

5. Date of next meeting

_____

Appendix II

MEETING OF THE OIE AD HOC GROUP ON ANTIMICROBIAL RESISTANCE

Paris, 26–28 January 2005

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Appendix III

APPENDIX 3.9.3.

GUIDELINES FOR THE RESPONSIBLE AND PRUDENT USE OF ANTIMICROBIAL AGENTS IN VETERINARY MEDICINE

Article 3.9.3.1.

Purpose

These guidelines provide guidance for the responsible and prudent use of antimicrobials in veterinary medicine, with the aim of protecting both animal and human health. The competent authorities responsible for the registration and control of all groups involved in the production, distribution and use of veterinary antimicrobials have specific obligations.

Prudent use is principally determined by the outcome of the marketing authorisation procedure and by the implementation of specifications when antimicrobials are administered to animals.

Article 3.9.3.2.

Objectives of prudent use

Prudent use includes a set of practical measures and recommendations intended to prevent and/or reduce the selection of antimicrobial-resistant bacteria in animals to:

1. maintain the efficacy of antimicrobial agents and to ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals;

2. comply with the ethical obligation and economic need to keep animals in good health;

3. prevent, or reduce, as far as possible, the transfer of bacteria (with their resistance determinants) within animal populations;

4. maintain the efficacy of antimicrobial agents used in food-producing animals ~~livestock~~;

5. prevent or reduce the transfer of resistant bacteria or resistance determinants from animals to humans;

6. maintain the efficacy of antimicrobial agents used in human medicine and prolong the usefulness of the antimicrobials;

7. prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);

8. protect consumer health by ensuring the safety of food of animal origin.

Appendix III (contd)

Article 3.9.3.3.

Responsibilities of the regulatory authorities

1. Marketing authorisation

The national regulatory authorities are responsible for granting marketing authorisation. This should be done in accordance with the provisions of the *Terrestrial Code.* They have a significant role in specifying the terms of this authorisation and in providing the appropriate information to the veterinarian.

2. Submission of data for the granting of the marketing authorisation

The pharmaceutical industry has to submit the data requested for the granting of the marketing authorisation. The marketing authorisation is granted only if the criteria of safety, quality and efficacy are met. An assessment of the potential risks and benefits to both ~~the~~ animals and humans ~~the consumer~~ resulting from the use of antimicrobial agents in food-producing animals should ~~must~~ be carried out. The evaluation should focus on each individual antimicrobial product and the findings not be generalised to the class of antimicrobials to which the particular active principle belongs. ~~If dose ranges or different durations of treatment are suggested~~, Guidance on usage should be provided for all dose ranges or different durations of treatment that are proposed.

3. Market approval

Regulatory authorities should attempt to expedite the market approval process of a new antimicrobial in order to address a specific need for the treatment of disease.

4. Registration procedures

Countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicinal products (VMPs), and whose supply principally depends on imports from foreign countries, should ~~must~~ undertake the following measures:

a) check the efficacy of administrative controls on the import of these VMPs;

b) check the validity of the registration procedures of the exporting and manufacturing country as appropriate;

c) develop the necessary technical co-operation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

Regulatory authorities of importing countries should request the pharmaceutical industry to provide quality certificates prepared by the competent authority of the exporting and manufacturing country as appropriate. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of unlicensed and counterfeit bulk active pharmaceutical ingredients and products.

5. Quality control of antimicrobial agents

Quality controls should be performed:

a) in compliance with the provisions of good manufacturing practices;

b) to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs;

c) to ensure that the quality and concentration (stability) of antimicrobial agents in the marketed dosage form(s) are maintained until the expiry date, established under the recommended storage conditions;

d) to ensure the stability of antimicrobials when mixed with feed or drinking water;

e) to ensure that all antimicrobials are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

6. Assessment ~~Control~~ of therapeutic efficacy

a) Preclinical trials

i) Preclinical trials should:

– establish the range of activity of antimicrobial agents on both pathogens and non-pathogens (commensals);

– assess the ability of the antimicrobial agent to select for resistance ~~resistant bacteria~~ *in vitro* and *in vivo,* taking into consideration pre-existing resistant strains;

– establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit the selection of antimicrobial resistance. ~~resistant bacteria~~. (Pharmacokinetic pharmacodynamic data and models can assist in this appraisal.)

ii) The activity of antimicrobial agents towards the targeted micro-organism ~~bacteria~~ should be established by pharmacodynamics. The following criteria should be taken into account:

– mode and spectrum of activity ~~action~~;

– minimum inhibitory and bactericidal concentrations;

– time- or concentration-dependent activity or co-dependency;

– activity at the site of infection.

iii) The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:

– bio-availability according to the route of administration;

– concentration of the antimicrobial at the site of infection and its distribution in the treated animal;

– metabolism that may lead to the inactivation of antimicrobials;

– excretion routes;

– use of combinations of antimicrobial agents should be scientifically supported ~~justified~~.

b) Clinical trials

Clinical trials should be performed to confirm the validity of the claimed therapeutic indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

i) diversity of the clinical cases encountered when performing multi-centre trials;

ii) compliance of protocols with good clinical practice, such as Veterinary International Cooperation on Harmonisation (VICH) guidelines;

Appendix III (contd)

iii) eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;

iv) parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

7. Assessment of the potential of antimicrobials to select for resistance ~~resistant bacteria~~

Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistance ~~resistant bacteria. The interpretation of their results should be undertaken with great caution.~~ The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered ~~Considerations may include:~~

a) the concentration of active compound in the gut of the animal (where the majority of potential food-borne pathogens reside) at the defined dosage level;

b) the route and level of human exposure to food-borne or other resistant organisms ~~bacteria~~;

c) the degree of cross-resistance within the class of antimicrobials and between classes of antimicrobials;

d) the pre-existing level of resistance in the pathogens of human health concern (baseline determination) in both animals and humans.

~~Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistant bacteria. The interpretation of their results should be undertaken with great caution.~~

8. Establishment of acceptable daily intake, maximum residue level and withdrawal periods for antimicrobial compounds

a) When setting the acceptable daily intake (ADI) and MRL for an antimicrobial substance, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.

b) The establishment of an ADI for each antimicrobial agent, and an MRL for each animal-derived food, should be undertaken.

c) For each VMP containing antimicrobial agents, withdrawal periods should be established in order to produce food in compliance with the MRL, taking into account:

i) the MRL established for the antimicrobial agent under consideration;

ii) the composition of the product and the pharmaceutical form;

iii) the target animal species;

iv) the dosage regimen and the duration of treatment;

v) the route of administration.

d) The applicant should provide methods for regulatory testing of residues in food.

9. Protection of the environment

An assessment of the impact of the proposed antimicrobial use on the environment should be conducted. Efforts should be made to ensure that the environmental impact of antimicrobial use ~~contamination with antimicrobials~~ is restricted to a minimum.

10. Establishment of a summary of product characteristics for each veterinary antimicrobial ~~medicinal~~ product (VAP)

The summary of product characteristics contains the information necessary for the appropriate use of VAPs ~~VMPs~~ and constitutes the official reference for their labelling and package insert. This summary should ~~always~~ contain the following items:

a) active ingredient and class,

b) pharmacological properties

c) any potential adverse effects,

d) target animal species,

e) therapeutic indications,

f) target micro-organisms ~~bacteria~~,

g) dosage and administration route,

h) withdrawal periods,

i) incompatibilities,

j) shelf-life ~~expiry date~~,

k) operator safety,

l) particular precautions before use,

m) particular precautions for the proper disposal of un-used or expired products,

n) information on conditions of use relevant to the potential for selection of resistance.

~~Antimicrobials that are considered to be important in treating critical diseases in humans should only be used in animals when alternatives are either unavailable or inappropriate.~~

~~Consideration should be given to providing such guidance by means of the product label and data sheet.~~

~~The oral route should be used with caution.~~

11. Post-marketing antimicrobial surveillance

The information collected through existing pharmacovigilance programmes, including lack of efficacy, should form part of the comprehensive strategy to minimise antimicrobial resistance. In addition to this the following should be considered:

a) General epidemiological surveillance

The surveillance of animal bacteria resistant to antimicrobial agents is essential. The relevant authorities should implement a programme according to the *Terrestrial Code*.

Appendix III (contd)

b) Specific surveillance

Specific surveillance to assess the impact of the use of a specific antimicrobial may be implemented after the granting of the marketing authorisation The surveillance programme should evaluate not only resistance development in target animal pathogens, but also in food-borne pathogens and/or commensals. Such surveillance will also contribute to general epidemiological surveillance of antimicrobial resistance.

12. Supply and administration ~~Distribution~~ of the antimicrobial agents used in veterinary medicine

The relevant authorities should ensure that all the antimicrobial agents used in animals are:

a) prescribed by a veterinarian or other ~~suitably trained and~~ *authorised* person;

~~b) delivered by an authorised animal health professional~~;

b) supplied only through licensed/authorised distribution systems;

c) administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons.

d) the relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired VAPs.

13. Control of advertising

All advertising of antimicrobials should be controlled by a code of advertising standards, and the relevant authorities must ensure that the advertising of antimicrobial products:

a) complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;

b) is restricted to authorised professionals, according to national legislation in each country.

14. Training of antibiotic users

The training of users of antimicrobials ~~antibiotic users~~ should involve all the relevant organisations, such as regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, veterinary professional organisations and other approved users such as food-animal owners. This training should focus on:

a) information on disease prevention and management strategies,

b) the ability of antimicrobials to select for resistance in food-producing animals,

c) the need to observe responsible use recommendations for the use of antimicrobial agents in animal husbandry in agreement with the provisions of the marketing authorisations

15. Research

The relevant authorities should encourage public- and industry-funded research.

Article 3.9.3.4.

Responsibilities of the veterinary pharmaceutical industry

1. Marketing authorisation of VAPs ~~VMPs~~

   The veterinary pharmaceutical industry has responsibilities to:

   a) supply all the information requested by the national regulatory authorities;

   b) guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices;

   c) implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance.

2. Marketing and export of VAPs ~~VMPs~~

   For the marketing and export of VAPs ~~VMPs~~:

   a) only licensed and officially approved VAPs ~~VMPs~~ should be sold and supplied, and then only through licensed/authorised distribution systems;

   b) the pharmaceutical industry should provide quality certificates prepared by the Competent Authority of the exporting and/or manufacturing countries to the importing country ~~only VMPs that have been authorised in the (exporting) country in which the product(s) is approved for sale or the quality of which is certified by a regulatory authority should be exported~~;

   c) the national regulatory authority should be provided with the information necessary to evaluate the amount of antimicrobial agents marketed.

3. Advertising

   The veterinary pharmaceutical industry should:

   a) disseminate information in compliance with the provisions of the granted authorisation;

   b) ensure that the advertising of antimicrobials directly to the food animal ~~livestock~~ producer is discouraged.

4. Training

   The veterinary pharmaceutical industry should participate in training programmes as defined in point 14 of Article 3.9.3.3.

5. Research

   The veterinary pharmaceutical industry should contribute to research as defined in point 15 of Article 3.9.3.3.

Article 3.9.3.5.

Responsibilities of wholesale and retail distributors ~~pharmacists~~

1. Retailers distributing VAPs ~~Pharmacists~~ should only do so on the prescription of a veterinarian or other suitably trained person authorised in accordance with national legislation and all products should be appropriately labelled ~~distribute veterinary antimicrobials on prescription. All products should be appropriately labelled (see point 5 of Article 3.9.3.6.)~~.

Appendix III (contd)

2. The guidelines on the responsible use of antimicrobials should be reinforced by retail distributors ~~pharmacists~~ who should keep detailed records of:

   a) date of supply,

   b) name of prescriber,

   c) name of user,

   d) name of product,

   e) batch number,

   f) quantity supplied.

3. Distributors ~~Pharmacists~~ should also be involved in training programmes on the responsible use of antimicrobials, as defined in point 14 of Article 3.9.3.3.

Article 3.9.3.6.

Responsibilities of veterinarians

The ~~prime~~ concern of the veterinarian is to promote public health and animal health and welfare. The veterinarian's responsibilities include preventing, identifying and treating animal diseases. The promotion of sound animal husbandry methods, hygiene procedures and vaccination strategies (good farming practice) can help ~~encourage good farming practice in order~~ to minimise the need for antimicrobial use in food-producing animals ~~livestock~~.

Veterinarians should only prescribe antimicrobials for animals under their care.

1. Use of antimicrobial agents

   The responsibilities of veterinarians ~~in this area~~ are to carry out a proper clinical examination of the animal(s) and then:

   a) only prescribe antimicrobials when necessary;

   b) make an appropriate choice of the antimicrobial based on experience of the efficacy of treatment.

   ~~On certain occasions, a group of animals that may have been exposed to pathogenic bacteria may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing to prevent the development of clinical disease and for reasons of animal welfare.~~

2. Choosing an antimicrobial agent

   a) The expected efficacy of the treatment is based on:

      i) the clinical experience of the veterinarian;

      ii) the activity towards the pathogens ~~pathogenic bacteria~~ involved;

      iii) the appropriate route of administration;

      iv) known pharmacokinetics/tissue distribution to ensure that the selected therapeutic agent is active at the site of infection;

      v) the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogens ~~pathogenic bacteria~~ involved.

   Should a first-line antibiotic treatment fail or should the disease recur, a second line treatment should ideally be based on the results of diagnostic tests.

To minimise the likelihood of antimicrobial resistance developing, it is recommended that antimicrobials be targeted to pathogens ~~bacteria~~ likely to be the cause of infection.

On certain occasions, a group of animals that may have been exposed to pathogens may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing to prevent the development of clinical disease and for reasons of animal welfare.

b) Use of combinations of antimicrobial agents should be scientifically supported. Combinations of antimicrobials may be ~~are~~ used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity. ~~Furthermore, the use of combinations of antimicrobials can be protective against the selection of resistance in cases in which bacteria exhibit a high mutation rate against a given antimicrobial.~~

~~Some combinations of antimicrobials may, in certain cases, lead to an increase in the selection of resistance.~~

3. Appropriate use of the antimicrobial agent chosen

A prescription for antimicrobial agents should ~~must~~ indicate precisely the treatment regime, the dose, the treatment ~~dosage~~ intervals, the duration of the treatment, the withdrawal period and the amount of drug to be delivered, depending on the dosage and the number of animals to be treated.

The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used. It is the veterinarian's responsibility to define the conditions of responsible use in such a case including the therapeutic regimen, the route of administration, and the duration of the treatment. ~~As far as 'Off label use' (extra label use) of veterinary medicinal products is concerned, although all medicinal products should be prescribed and used in accordance with the specifications of the marketing authorisation, the prescriber should have the discretion to adapt these in exceptional circumstances~~.

4. Recording

Records on veterinary antimicrobial drugs should be kept in conformity with national legislation. Information records should include the following ~~All available information should be consolidated into one form or database. This information should~~:

a) ~~allow monitoring of the~~ quantities of medication used;

b) ~~contain~~ a list of all medicines supplied to each food-producing animal ~~livestock~~ holding;

c) ~~contain~~ a list of medicine withdrawal periods ~~and a system for allowing information to be updated~~;

d) ~~contain~~ a record of antimicrobial susceptibilities;

e) ~~provide~~ comments concerning the response of animals to medication;

f) ~~allow~~ the investigation of adverse reactions to antimicrobial treatment, including lack of response due to antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

Veterinarians should also periodically review farm records on the use of VAPs to ensure compliance with their directions and use these records to evaluate the efficacy of treatment regimens.

Appendix III (contd)

5. Labelling

All medicines supplied by a veterinarian should be ~~adequately~~ labelled according to national legislation ~~with the following minimum information:~~

~~a) the name of the owner/keeper or person who has control of the animal(s);~~

~~b) the address of the premises where the animal(s) is kept;~~

~~c) the name and address of the prescribing veterinarian;~~

~~d) identification of the animal or group of animals to which the antimicrobial agent was administered;~~

~~e) the date of supply;~~

~~f) the indication 'For animal treatment only';~~

~~g) the warning 'Keep out of the reach of children';~~

~~h) the relevant withdrawal period, even if this is nil.~~

~~The label should not obscure the expiry date of the preparation, batch number or other important information supplied by the manufacturer~~.

6. Training

Veterinary professional organisations should participate in the training programmes as defined in point 14 of Article 3.9.3.3. It is recommended that veterinary professional organisations develop for their members species-specific clinical practice guidelines on the responsible use of VAPs.

Article 3.9.3.7.

Responsibilities of food-animal ~~livestock~~ producers

1. Food-animal ~~Livestock~~ producers with the assistance of a veterinarian, ~~where possible,~~ are responsible for ~~preventing outbreaks of disease and~~ implementing health and welfare programmes on their farms (good farming practice) in order to promote animal health.

2. Food-animal ~~Livestock~~ producers should ~~have to~~:

   a) draw up a health plan with the attending veterinarian ~~in charge~~ that outlines preventative measures (feedlot health plans, mastitis control plans, endo- and ectoparasite control ~~worming~~ and vaccination programmes, etc.);

   b) use antimicrobial agents only on prescription, and according to the provisions of the prescription;

   c) use antimicrobial agents in the species, for the uses and at the dosages ~~doses~~ on the approved/registered labels and in accordance with product label instructions or the advice of a veterinarian familiar with the animals and the production site;

   d) isolate sick animals, when appropriate, to avoid the transfer of pathogens ~~resistant bacteria~~. Dispose of dead or dying animals promptly under conditions approved by the relevant authorities;

   e) comply with the storage conditions of antimicrobials in the rearing unit, according to the provisions of the leaflet and package insert;

f) address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated;

g) comply with the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;

h) dispose of surplus antimicrobials under safe conditions for the environment; ~~partially-used~~ medicines should only be used within the expiry date, for the condition for which they were prescribed and, if possible, in consultation with the prescribing veterinarian;

i) maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the veterinarian responsible for treating the animals;

j) keep adequate records of all medicines used, including the following:

   i) name of the product/active substance and batch number,

   ii) name of prescriber and/or the supplier,

   iii) date of administration,

   iv) identification of the animal or group of animals to which the antimicrobial agent was administered,

   v) ~~diagnosis/~~clinical conditions treated,

   vi) dosage ~~quantity of the antimicrobial agent~~ administered,

   vii) withdrawal periods,

   viii) result of laboratory tests,

   ix) effectiveness of therapy;

k) inform the responsible veterinarian of recurrent disease problems.

Appendix IV

CRITICALLY IMPORTANT VETERINARY ANTIMICROBIALS

1. Background

The FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance held in Geneva, Switzerland, in December 2003 (Scientific Assessment) and in Oslo, Norway, in March 2004 (Management Options) recommended that the OIE should develop a list of critically important antimicrobials in veterinary medicine and that WHO should also develop such a list of critically important antimicrobials in human medicine.

Conclusion No. 5 of the Oslo Workshop is as follows:

5. The concept of "critically important" classes of antimicrobials for humans should be pursued by WHO. The Workshop concluded that antimicrobials that are critically important in veterinary medicine should be identified, to complement the identification of such antimicrobials used in human medicine. Criteria for identification of these antimicrobials of critical importance in animals should be established and listed by OIE. The overlap of critical lists for human and veterinary medicine can provide further information, allowing an appropriate balance to be struck between animal health needs and public health considerations.

The following terms of reference for the proposed OIE Expert Group on Veterinary Critically Important Antimicrobials (VCIA) were adopted in November 2005 by the OIE Ad hoc group on antimicrobial resistance.

2. Approved terms of reference for the proposed OIE Expert Group on Veterinary Critically Important Antimicrobials (VCIA)

This Expert Group should consider recent recommendations and texts (including FAO/OIE/WHO Workshops) relating to the establishment of a list of VCIA.

Mission

To propose a methodology for establishing a list of VCIA.

- In order to do so, the Expert Group should first define the criteria that should be taken into account, if possible in coordination with WHO.

- The Expert Group should examine the different criteria that could apply to the veterinary list.

Procedure

Considering the current definition of antimicrobials given by the OIE Ad hoc Group on Antimicrobial Resistance at its meeting of 15–17 November 2004:

- Identify relevant species (food-producing, companion animals and aquatic species) in which antimicrobials are used.

- Consult appropriate bodies (OIE Member Countries, veterinarians, industry, regulatory authorities) in establishing the list. This consultation phase is considered essential.

The Expert Group should also consider and take into account:

- The major diseases of animals, including aquatic animals,

- The approved products and their condition of use (species, route of administration, diseases),

Appendix IV (contd)

- The possible alternative antimicrobial options and management strategies,
- Cross and co-resistance between antimicrobials,
- The economic costs (diseases, antimicrobials),
- Animal welfare aspects,
- The situation in different countries.

Outcome

- Establish criteria for the establishment of a list of VCIA.
- Consider the feasibility of a global list versus local (national) or regional lists.
- Consider, in co-operation with WHO, classification systems for antimicrobials (classes, chemical form and international units).
- Provide a list of VCIA.

3. Aim of the list of VCIA

Veterinary antimicrobial products (VAPs) are essential tools for treating, controlling and preventing infectious animal diseases as well as promoting animal health and welfare and consequently human health.

The aim of defining a list of VCIA is to safeguard the efficacy and availability of VAPs for diseases where there are few or no antimicrobial alternatives. Inclusion implies that the disease is serious and may have important consequences in term of animal health and welfare and/or public health and/or important economic consequences.

The list could help the veterinarian in their therapeutic choice.

The list could complement the OIE guideline for the responsible and prudent use of antimicrobial agents in veterinary medicine (OIE *Terrestrial Code* Appendix 3.9.3). This guideline indicates at article 3.9.3.6 the responsibilities of veterinarians: “Should a first line antibiotic treatment fail or recur, a second line treatment should ideally be based on the result of diagnostic tests.”

The list could be useful for the risk assessment of antimicrobial resistance in accordance with OIE *Terrestrial Code* Appendix 3.9.4. In this context, lists of CIA for humans and for animals are elements that could be taken into account in a risk assessment process.

4. Proposed criteria for establishing a CIA list for veterinary medicine

There are various grounds by which VAPs may be defined as V-CIA, but one of the main criteria should be that there are few or no antimicrobial alternatives for the treatment, control and/ or prevention of animal disease.

If the antimicrobials are defined as critically important, this implies that the disease they are used to treat or prevent is serious and may have important consequences in term of animal health and welfare and/or public health and/or important economical consequences.

Proposed definition of V-CIA:

Veterinary critically important antimicrobials are antimicrobials used for the treatment, prevention and control of serious animal infections that may have important consequences for animal health and welfare, public health or important economical consequences and where there are few or no alternatives.

These antimicrobials should be available in adequate amounts and appropriate pharmaceutical forms, be of assured quality and economically accessible.

Primary criteria

- Used to treat serious disease in an animal species.
- Sole therapy or one of few antimicrobial alternatives.

Additional criteria that could be considered:

- Assured quality.
- Appropriate dosage form.
- Availability.
- Economic considerations/ accessibility.

5. Responsibility for the establishment and maintenance of the list

National or regional authorities should transmit their lists to OIE for review and consolidation purposes. OIE will maintain a consolidated list of antimicrobial active substances considered as V-CIA.

The list should be regularly updated.

The responsibility to define what medicinal products containing antimicrobials are considered as essential remains a national or regional responsibility.

6. Methodology

The establishment of a list of V-CIA should be undertaken through extensive consultation with all stakeholders.

It should include:

- Sending of a questionnaire to OIE member countries.
- Establishment of a public call for contributions on the OIE website.

At a later stage, establishment of an electronic discussion forum managed by an OIE Collaborating Centre may be considered.

7. Proposed questionnaire

A draft questionnaire regarding V-CIA will be produced by the OIE Collaborating Centre at AFSSA, Fougères, with the assistance of two experts from the Ad hoc Group (Dr Liisa Kaartinen and Dr Chris Teale). The draft will be sent to OIE Ad hoc Group on Antimicrobial Resistance for endorsement. Once finalised, it will be sent to OIE Member Countries.

Appendix IV (contd)

8. Proposed timetable

After discussion with Dr Bernard Vallat, OIE Director General, it was decided that the questionnaire could be prepared within 2 months by the Group and then sent for approval to the President of the OIE Biological Standards Commission, to allow for fast consultation of the OIE Member Countries and other stakeholders.

Appendix V

CLASSIFICATION OF ANTIMICROBIALS

Penicillins	*Natural penicillins*
	Antistaphylococcal penicillins (Beta-lactamase sensitive penicillins)
	Penicillins with extended spectrum
	Antipseudomonal and ureido penicillins
	Beta-lactamase resistant penicillins
Cephalosporins	*Cephalosporins – 1st generation*
	Cephalosporins – 2nd generation + cephamycins
	Cephalosporins – 3rd generation
	Cephalosporins – 4th generation
Monobactams	
Carbapenems	
Aminoglycosides	*Streptomycin group*
	Deoxystreptamine group
Macrolides	*C14*
	C16
	Azalides
Ketolides	
Lincosamides	
Streptogramins	
Pleuromutilins	
Tetracyclines	
Phenicols	
Quinolone	1st generation
	2nd generation Fluoroquinolones
Furans	
Trimethoprim	
Sulfonamides	
Polymyxins Cyclic lipopeptides	
Glycopeptides	
Nitro 5 imidazoles	
Ansamycins	
Fusidic Acid	
Fosfomycin	
Oxazolidinones	
Coumarinic Antibiotics	
Orthosomycins	
Cyclic peptides	
Ionophores peptides	