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## REPORT OF THE MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION

Paris, 22–24 January 2008

The OIE Biological Standards Commission met at the OIE Headquarters from 22 to 24 January 2008. Dr Bernard Vallat, Director General of the OIE, welcomed the Members of the Commission, Professor Steven Edwards, President, Dr Beverly Schmitt, Vice-President and Dr Mehdi El Harrak, Secretary General as well as the other expert participant, Dr Peter Wright. The other members of the Commission (Dr Santanu K. Bandhopadhyay and Dr Vladimir Drygin) were invited but could not attend the meeting.

Following his welcome, Dr Vallat asked the Commission to give priority to the following points:

- the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)* chapter on bluetongue should reflect the latest and best available information on vaccines and vaccination;
- the work programme for OFFLU<sup>1</sup> to ensure the network is fully effective;
- how best to update the list of antimicrobials of veterinary importance;
- to define key priorities for attention by the *ad hoc* Group on Biotechnology.

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:

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

*OIE Collaborating Centre for Surveillance and Control of Animal Protozoan Diseases*  
National Research Center for Protozoan Diseases, Obihiro University of Agriculture and Veterinary Medicine, Japan  
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*OIE Reference Laboratory for Foot and mouth disease*  
Laboratorio de Fiebre Aftosa de la Dirección de Laboratorios y Control Técnico, ARGENTINA  
Tel./Fax: (+54-11) 4836.1115/0066; E-mail: dilab@senasa.gov.ar  
Designated Reference Expert: Eduardo D. Maradei

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1 OFFLU: OIE/FAO Network on Avian Influenza

The Commission agreed in principle to this proposal but suggested that the title be changed to specify laboratory capacity building.

*OIE Collaborating Centre for Laboratory Enhancement*

Australian Animal Health Laboratory (AAHL), Geelong, AUSTRALIA

Tel: (61.3) 52.27.50.14; Fax: (61.3) 52.27.52.50; E-mail: peter.daniels@csiro.au

## 1.2. Review of twinning applications

The Commission reiterated its opinion that twinning projects are open to OIE Collaborating Centres as well as Reference Laboratories, particularly where the collaborating centre is laboratory-based. Priority areas for Collaborating Centre twinning projects are avian influenza, training and veterinary medicines.

A number of expressions of interest have been noted, and the Commission urges all involved to move forward as quickly as possible with their applications so that best use can be made of the available funds. Two full applications were approved in principle for twinning projects:

Avian influenza and Newcastle disease: Istituto Zooprofilattico Sperimentale delle Venezie (IZSVE), Italy and the National Center for Animal And Plant Health (CENSA), San José de las Lajas, La Habana, Cuba. Having reviewed the application, the Commission asked the officer in charge of OFFLU twinning (Dr Keith Hamilton) to clarify certain aspects.

Brucellosis: Istituto Zooprofilattico Sperimentale dell’Abruzzo e del Molise ‘G. Caporale’, Teramo, Italy and the National Veterinary Laboratory, Asmara, Eritrea. Again some points of clarification were requested. The Commission noted that applications where the “parent” laboratory is not an OIE Reference Laboratory for the disease (or a Collaborating Centre in a related area) were outside the scope of the scheme. It also expressed concern that individual Reference Laboratories should not over commit by taking on too many twinning arrangements.

## 1.3 Annual Reference Laboratories/Collaborating Centre reports for 2007 for terrestrial animal diseases

Reports had been received from 136/142 Reference Laboratories and 23/23 Collaborating Centres for terrestrial animal diseases. The Commission expressed its ongoing appreciation of the enthusiastic support and expert advice given to OIE by the Reference Laboratories and Collaborating Centres. The full set of reports will be supplied to Member Countries and to all the Reference Laboratories and Collaborating Centres on a CD-ROM as well as in printed format for those Member Countries that prefer to receive a hard copy. The international activities relevant to the work of the OIE are summarised in the table:

**Reference Laboratories**

<b>General activities</b>		<b>Percentage of Laboratories carrying out these activities</b>
1	Test(s) in use/or available for the specified disease	99%
2	Production and distribution of diagnostic reagents	88%
<b>Specific OIE activities</b>		
3	International harmonisation/standardisation of methods	74%
4	Preparation and supply of international reference standards	61%
5	Research and development of new procedures	88%
6	Collection, analysis and dissemination of epizootiological data	69%
7	Provision of consultant expertise	73%
8	Provision of scientific and technical training	74%
9	Provision of diagnostic testing facilities	60%
10	Organisation of international scientific meetings	39%
11	Participation in international scientific collaborative studies	66%
12	Presentations and publications	90%

## 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	95%
2 Proposal or development of any procedure that will facilitate harmonisation of international regulations applicable to the surveillance and control of animal diseases, food safety and animal welfare	82%
3 Placement of expert consultants at the disposal of the OIE	82%
<b>Specific OIE activities</b>	
4 Provision of scientific and technical training within to personnel from OIE Member Countries	77%
5 Organisation of scientific meetings on behalf of the Office	46%
6 Coordination of scientific and technical studies in collaboration with other laboratories or organisations	82%
7 Publication and dissemination of any information that may be useful to OIE Member Countries	91%

### 1.4. Technical Item and Resolution adopted in May 2007 on the role of Reference Laboratories and Collaborating Centres in Providing Permanent Support for the Objectives and Mandates of the OIE

The Commission reviewed and endorsed the Technical Item report submitted by Dr Gajadhar. Resolution XXXIV adopted by the International Committee in May 2007, strongly supports the work that the Commission is taking forward with Reference Laboratories and Collaborating Centres, and it did not identify any changes needed in the mandates. This could be discussed further at the Conference of Reference Laboratories and Collaborating Centres to be held in Spain in 2009.

## 2. International standardisation of diagnostic tests and vaccines

### 2.1. OIE standardisation programmes for diagnostic tests

*Highly pathogenic avian influenza (HPAI) – Coordinator: Dr P. Selleck, Australian Animal Health Laboratory (AAHL), Geelong, Victoria, Australia*

Dr Selleck had reported that a candidate reference serum for the avian influenza (AI) AGID<sup>2</sup> test had now prepared and he will soon send it to the other Reference Laboratories for evaluation. This and other needs for AI test standardisation will be discussed at a meeting of the OIE AI experts due to be held at the OIE headquarters in March.

*Rabies – Coordinator: Dr A. Fooks, VLA Weybridge, UK*

Dr Fooks is working with the Chinese laboratory on the preparation of weak positive canine sera.

*Enzootic bovine leukosis (EBL) PCR procedure – Coordinator: Dr T. Vahlenkamp, Friedrich Loeffler Institute, Greifswald-Insel, Germany*

Following changes of experts at the Reference Laboratories, Dr Vahlenkamp had agreed to take on leadership of the project to develop a standard PCR protocol.

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

Mrs Stack reported that the interlaboratory comparison had been carried out and that the data collected was currently being analysed.

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2 AGID: agar gel immunodiffusion

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

Dr Nielsen reported that the OIE international porcine brucellosis Standard serum has been prepared and evaluated. The data is being analysed with the caprine and ovine data.

#### *Dourine*

There had been no progress with the project to develop international standards for dourine. The Commission would request the newly designated Collaborating Centre for Animal Protozoan Diseases in Japan to take forward the characterisation of an acceptable standard strain of *Trypanosoma equiperdum* and to develop internationally validated standard reference sera for dourine.

### **3. List of prescribed and alternative tests**

#### **3.1. Gamma interferon test for bovine tuberculosis**

The Commission had requested advice from the OIE Reference Laboratory experts on the suitability of proposing the gamma interferon as a prescribed test for bovine tuberculosis. Based on the answers received, the Commission recommends that the test be designated at this stage as an alternative test for trade. As the test is only available as a commercial kit, the manufacturer would be encouraged to apply to have the kit included on the OIE register, which would give the opportunity for a fuller evaluation of its validation data. Considering the wider use of the gamma interferon test for diagnosis and surveillance, the Commission noted that the test has higher sensitivity but lower specificity than the tuberculin test and as such might be better used as a screening test with the tuberculin test being used for confirmation. At present, the tests are often used in the reverse manner, which seems inappropriate. It is nevertheless important to take account of practical considerations such as general familiarity with the tuberculin test, and the difficulty in some countries of getting blood samples to the laboratory in time to preserve their lymphocyte viability, which is an essential component of the test.

The Commission also received a report from Dr Lea Knopf on her two missions to Africa on the establishment of an African research network on bovine TB. Tuberculosis in both cattle and humans is a major problem in Africa. The role of both tuberculin testing, especially applicability of standard cut offs for doubtful and positive reactions and use of gamma interferon tests in the African context was discussed, and the Commission informed Dr Knopf that there is very little information on the skin test responses of certain African cattle breeds. There is a need for further research on this.

#### **3.2. Prescribed tests for African horse sickness**

The OIE experts had been asked to suggest a suitable prescribed test for agent identification in African horse sickness in light of the requirements in the proposed new *Terrestrial Animal Health Code (Terrestrial Code)* chapter. Should that chapter be adopted in May 2008 and taking into consideration the advice received, the Commission would recommend that the real-time PCR<sup>3</sup> be adopted as an alternative test for trade. The validation data seen by the Commission was insufficient to justify its designation as a Prescribed Test.

#### **3.3. Serological tests for equine trypanosomosis**

Further advice and some published papers had been provided by Dr Louis Touratier, co-ordinator of the OIE *ad hoc* Group on Non-tsetse transmitted animal trypanosomosis. The Commission noted with interest the comparisons between complement fixation, card agglutination, ELISA<sup>4</sup>, and an immune trypanolysis test. The latter showed very good diagnostic performance but the Commission felt it to be too specialised for general use. Further conclusions must await the results of the standardisation initiative (see section 2.1 above).

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3 PCR: polymerase chain reaction

4 ELISA: enzyme-linked immunosorbent assay

## 4. Expert, *Ad hoc* and Working Groups

### 4.1. Report of the Meeting of the *ad hoc* Group on Biotechnology

The report of the meeting held from 28 to 30 November 2007 was accepted and is included as [Appendix III](#) of this report, for Member Country comments. It was recommended that future work of the Group should be carried out through a series of smaller, specialised subgroups. The Commission determined the following priorities for future work:

- Applications of biotechnology to molecular diagnostics.
- RNA-based technologies.
- Vaccinology, in particular the use of genetically modified and recombinant DNA vaccines and their implications for food safety and animal health.
- The implications of biotechnology, and genetic engineering in particular, for animal health and welfare.

The Commission endorsed the recommendation of the *ad hoc* Group that OIE should consider whether there are any issues related to food safety, animal health or welfare, in the case of animals treated with non-heritable DNA constructs (including recombinant vaccines). Experts from WHO<sup>5</sup> and FAO<sup>6</sup> should be invited to attend this discussion.

Dr Anne MacKenzie had prepared a paper on “Potential Nanotechnology Applications in Animal Health”, which sets out some key issues that Delegates should consider. This will be referred to the Publications Dept for consideration. In addition she had prepared a shorter paper on “Nanotechnologies in diagnosis and vaccine development”. This is included with this report ([Appendix IV](#)) for Member Country comment and eventual inclusion in the updated web version of the *Terrestrial Manual* subject to adoption in May 2008.

### 4.2. Report of the Meeting of the Expert Surveillance Panel on Equine influenza

The Commission reviewed and endorsed the 2008 report of the equine influenza expert surveillance panel, which can be found at [Appendix V](#). 2007 was a significant year for equine influenza. Vaccine manufacturers and regulatory authorities are urged to take note of the recommendations, in particular regarding the strains to be included in this year’s equine influenza vaccines. The key recommendations will also be published in the OIE *Bulletin*.

### 4.3. *Ad hoc* Group on diseases of dromedaries

The Commission agreed that the remit of this *ad hoc* Group should cover all Camelidae and not be limited to dromedaries. Dr El Harrak (Secretary General of the Biological Standards Commission) was appointed Chairman of the Group. Three other experts were identified and would be contacted. The first meeting of the Group will be held this year. The Group would be asked to identify important diseases of camels and to propose specific diagnostic techniques to be developed. There is a meeting on camelidae in 2009 in Tunisia and this would present a good opportunity to meet other experts, to exchange information and to collaborate on this topic.

### 4.4. *Ad hoc* Group on Antimicrobial Resistance

Dr Tomoko Ishibashi updated the Commission on an OIE/WHO meeting on critically important antimicrobials that she had attended in November 2007. The Commission proposed that the OIE Reference Laboratory on Antimicrobial Resistance would be responsible for reviewing the list of antimicrobials of veterinary importance and proposing modifications for adoption. Any changes adopted in accordance with the OIE procedures would be added to the list on the web. There is no requirement at present for the *ad hoc* Group to reconvene.

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5 WHO: World Health Organization

6 FAO: Food and Agriculture Organization of the United Nations

#### **4.5. Ad hoc Group on Validation**

Following the workshop on diagnostic test validation held during the WAVLD<sup>7</sup> Symposium in Melbourne, the Commission identified the need for an *ad hoc* Group on Validation to develop guidelines on how to apply the OIE validation template to different types of test (e.g. serological, PCR, TSE<sup>8</sup>, etc.). Possible names of participants were suggested, and the first meeting should be held in June 2008 if possible.

### **5. OIE Register of diagnostic tests**

#### **5.1. OIE Validation template and application procedure**

Dr François Diaz updated the Commission on the outcome of a meeting with the AEFRV<sup>9</sup>, held in September 2007 at the OIE headquarters. Dr Vallat had agreed to reduce the initial application fee for the OIE Register. Based on feedback from AEFRV, the OIE validation template has been simplified and clarified. The Commission endorsed the new template and asked that it be put on the OIE website. A series of guidelines is needed to assist applicants with completion of the template (see item 4.5). The AEFRV had requested that kits should be placed on the OIE Register upon satisfactory completion of the evaluation procedure, including endorsement by the Commission, without having to wait for adoption by the International Committee. The OIE Director General rejected this proposal.

#### **5.2. Abstract of the validation studies led by Bio-Rad for their kit Platelia Rabies II**

A recommendation of the AEFRV meeting was that the OIE register should include on the website an abstract sheet summarising the validation data for the kit. An abstract sheet template has thus been developed and was applied to the first kit on the OIE register. The Commission agreed.

#### **5.3. OIE Procedure - Final assessment report**

Since the last meeting, Prof Edwards confirmed that the Commission had endorsed by email the experts report on the “BioChek Avian Influenza Antibody test kit” for avian influenza. This will be recommended to the International Committee for inclusion on the OIE Register.

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

#### **6.1 Finalisation of the sixth edition**

For this agenda item, the Commission was joined by the Consultant Editor, Dr James Pearson.

The sixth edition had been adopted by the International Committee in May 2007 with the proviso that the Commission could make last minute changes in line with Member Country comments. Dr Pearson sought advice on a number of chapters that had received a large number of Member Country comments. A few chapters were awaiting final agreement by the authors. It is aimed to publish this edition by May 2008.

#### **6.2. Strategy for future editions**

Prof Edwards noted the increasing burden on a very small team of keeping the *Terrestrial Manual* up to date with the latest technology. He felt the current pattern of a publishing a completely new edition every four years was becoming unmanageable. The Commission agreed and suggested that each year a set of chapters should be identified that were in need of priority revision. These would be updated in the web version of the *Terrestrial Manual*. The production of new printed editions at 4-yearly intervals could continue according to the directions from OIE, but this would be an accumulation of the annual updates rather than a complete revision of the whole *Terrestrial Manual*.

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7 WAVLD: World Association of Veterinary Laboratory Diagnosticians

8 TSE: transmissible spongiform encephalopathies

9 AEFRV : European Association of Veterinary Diagnostics Manufacturers

Accordingly the Commission identified chapters that should be revised during 2008 for presentation to the Committee in May 2009. Delegates would be invited to suggest chapters needing priority revision.

## **7. Liaison with other Commissions and Groups**

### **7.1. Scientific Commission for Animal Diseases**

The Scientific Commission had transferred some Member Country comments on proposed *Terrestrial Code* chapters on bovine tuberculosis and classical swine fever to the Biological Standards Commission. For bovine tuberculosis, two Member Countries had asked that the gamma interferon be considered for adoption as a prescribed test. The Commission had already discussed this (see item 3.1.) and would convey its opinion to the Scientific Commission. For classical swine fever, the Commission agreed with Member Country comments that reverse-transcription PCR should be included in the surveillance guidelines as a practical tool.

The President of the Scientific Commission had indicated that he had some concerns with the vaccine section of the chapter on bluetongue for the *Terrestrial Manual*. The Commission requested details of the text in question. Once this is received, the Commission and the Consultant Editor would review the chapter and amend, if necessary.

### **7.2. Terrestrial Animal Health Standards Commission**

The Commission had received comments from one Member Country on the guidelines on somatic cell nuclear transfer that had been developed by the *ad hoc* Group on Biotechnology. As agreed at the last meeting, these guidelines would be proposed for adoption and eventual inclusion in the *Terrestrial Code*. The comments and any other that may be received would be passed to the Code Commission for further action.

In follow-up to the last joint meeting, the Biological Standards Commission reiterated its earlier advice on paratuberculosis, that there are still no robust and well validated diagnostic tests; and on Agent Id tests for African horse sickness (see item 3.2). Regarding equine rhinopneumonitis caused by EHV-1, the Commission advised the Code Commission, based on advice from experts, that a useful description of suspect clinical signs would be, "pyrexia, nasal discharge, recent unexplained abortion, and/or hind limb ataxia of undetermined cause".

The Commission noted a report of a meeting of the International Embryo Transfer Society in which IETS proposes some additions to the *Terrestrial Code* chapters on contagious caprine pleuropneumonia.

## **8. Any other business**

### **8.1. Update on OFFLU**

Dr Keith Hamilton updated the Commission on the activities of OFFLU. The Steering Committee had recommended a restructuring of the network committee structure, which had now been implemented. In addition, the secretariat would now be based at the OIE Headquarters hopefully for the next 3 years. Avian influenza continues to be a matter of international concern, and a number of specialist working groups would be formed within OFFLU to deal with critical aspects of the science. An OFFLU-funded scientist was now in post and will be working on bioinformatics, liaising with all the OIE Reference Laboratories. Working groups proposed so far included a meeting of OIE Reference Laboratory experts on 5 March, at the OIE Headquarters, a group on epidemiology and another on vaccination. The newly formed Executive Committee would consider other pressing needs.

### **8.2. Second Conference for OIE Reference Laboratories and Collaborating Centres, June 2009, Spain**

The WAVLD had agreed in principle that the next conference of OIE Reference Laboratories and Collaborating Centres could be held in conjunction with its next meeting in Madrid from 19 to 22 June, 2009 (<http://www.wavld2009.com/>). The Commission would take this forward at its next meeting.

### **8.3. Transport of infectious substances**

Drs Pearson and Hamilton reported on a meeting at WHO headquarters, Geneva, 12–14 Dec 2007 to review regulations for shipment of infectious substances. The Commission reiterated its earlier opinion that diagnostic specimens for submission to OIE Reference Laboratories must continue to be allowed to be shipped as Category B.

### **8.4. Biosecurity**

The Commission reiterated its view (see report for Sept. 2007) that the OIE Standards for Biosafety and Biosecurity as set out in the new chapter for the *Terrestrial Manual*, were appropriate and fit for purpose if properly applied. Dr Pearson reported on a subregional WHO workshop, where he had represented OIE, in Nairobi, Kenya in May 2007. He was disappointed at the poor attendance by veterinary laboratories from Africa, as the workshop had provided useful information including training on the packaging and shipment of Category A and Category B substances.

Dr Pearson also reported on a meeting at the National Institutes of Health, Bethesda, Maryland, USA on “Dual use issues in life sciences research”. The meeting emphasised the importance of codes of conduct for researchers to ensure that security was maintained without overly restricting legitimate studies.

### **8.5. Vaccines**

Dr Diaz reported on the first two days of the meeting of the OIE regional workshop on Harmonisation of Veterinary Vaccines at the Veterinary Biologics Assay Division, Bureau of Quality Control of Livestock Products, Pakchong, Thailand, 21–25 January 2008. He emphasised the great interest of the participants in both the OIE twinning initiative and the OIE standards on vaccines. He also reported that he had received numerous questions and comments on the OIE standards on vaccines.

### **8.6. Dates of next Biological Standards Commission meeting**

An extraordinary meeting by Teleconference will be arranged if necessary to deal with twinning applications. The next full meetings are planned for 23–25 September 2008 and 3–5 February 2009.

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.../Appendices



**MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION**

**Paris, 22–24 January 2008**

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**Agenda**

1. OIE Reference Laboratories and Collaborating Centres
2. International Standardisation of Diagnostic Tests and Vaccines
3. List of Prescribed and Alternative Tests
4. Expert, Ad hoc and Working Groups
5. OIE Register of diagnostic tests
6. *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*
7. Liaison with other Commissions
8. Any Other Business



**MEETING OF THE OIE BIOLOGICAL STANDARDS COMMISSION  
Paris, 22–24 January 2008**

**List of participants**

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**REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON BIOTECHNOLOGY**  
**Paris, 28–30 November 2007**

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A meeting of the OIE *ad hoc* Group on Biotechnology was held at the OIE Headquarters in Paris from 28 to 30 November 2007. The meeting was chaired by Prof. Sandor Belak. Dr Cyril G. Gay acted as rapporteur. The Agenda and List of Participants are given at Appendices I and II, respectively. It was recommended to hold the next meeting in October 2008.

**1. Introduction**

The *ad hoc* Group was welcomed by Dr Gideon Brückner, Head of the OIE Scientific and Technical Department, on behalf of Dr Bernard Vallat, Director General of the OIE.

Dr Brückner thanked Dr Anne MacKenzie for the position paper on Nanotechnologies, Dr Bruce Whitelaw for the position paper on RNA-based products, and Dr Gay for the organisation of the International Symposium on Animal Genomics for Animal Health. Dr Brückner requested that the Group identify one member to participate in the meeting of the OIE *ad hoc* Group on Traceability, which will be held in Paris in January 2008. Also, a representative from the OIE Animal Production Food Safety Working Group would participate in the OIE *ad hoc* Group on Biotechnology on 29 November for the purpose of coordinating the work of the respective *ad hoc* Groups.

Dr Brückner informed the Group that Dr Vallat had made the decision that all OIE *ad hoc* Groups should comprise a maximum of six members. This decision will enter into force for the next meeting of the Group. The Group agreed that Dr Belak should write a letter to Dr Vallat describing the restrictions for this Group that would ensue if it were limited to six members only because the complexities and scope of technical issues under discussion. The letter would provide some helpful suggestions for the implementation of the new quota.

**2. Review of the Terms of Reference: Proposals from Prof. Steve Edwards**

The *ad hoc* Group on Biotechnology discussed the proposals from Prof. Steve Edwards, President of the OIE Biological Standards Commission regarding the Group's Terms of Reference. The *ad hoc* Group felt that its tasks must be expanded to address the many issues that are currently evolving as a result of the promise offered by animal genomics, reproductive biotechnologies including transgenics, stem cells, nanotechnologies, and the continually emerging biotechnologies (such as RNA-based technologies) to proactively position the OIE as a leader in dealing with the issues most likely to have an impact on animal health and welfare in the 21<sup>st</sup> century. Therefore, the Group proposes several documents to address the most pressing issues (see Agenda Item 2.2).

In regard to DIVA<sup>1</sup> vaccines and companion diagnostic tests, the Group agreed that disease-specific guidance is important but felt that direction on general principles and standards is critically needed in order to advance the development of these countermeasures for the control and eradication of priority diseases. Issues include integrating in parallel vaccine and diagnostic development, negative versus positive markers, clear definition

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1 DIVA: Differentiating infected from vaccinated animals

of the expected DIVA vaccine and companion diagnostic profile, etc. The Group agreed that guidelines should be prepared and incorporated in the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)*, as either a revision of the chapter section or an expanded Appendix of Chapter 1.1.8 Biotechnology in the diagnosis of infectious diseases and vaccine development. Dr Gay was identified as the lead for writing this document.

With regard to new technologies for diagnostic discovery, the Group discussed the availability of rapid sequencers (454, Illumina) and their use in research laboratories such as the IAEA<sup>2</sup> in Vienna, Austria, and the evolution of the new field called “metagenomics”. The Group agreed to write a position paper on metagenomics as a diagnostic platform. Dr Belak nominated Dr Albert Osterhaus, Rotterdam, Netherlands, and Dr Gilles Aumont, INRA<sup>3</sup>, as co-leaders to write this position paper.

In regard to transgenic animals, the Group agreed to develop animal health guidelines and to propose a work plan/next steps.

The Group also discussed recent breakthroughs in stem cell technologies, such as the four genes platform for generating pluripotent cells, and the potential for this technology to revolutionise this field of research and possibly replace some of the current embryo-based technologies. The Group agreed that this topic should be 1) discussed in the transgenic animal position paper and 2) also as a separate position paper to address the various potential applications, such as cell treatment/tissue replacement and transgenic animals.

In response to the request from the Biological Standards Commission for a background paper on nanotechnologies, Dr MacKenzie had prepared a position paper (see Agenda Item 4).

The Group agreed to prepare and distribute all materials ahead of OIE *ad hoc* Group on Biotechnology scheduled meetings to allow participants to study and assess proposed documents and be prepared in time for the meeting.

#### **2.1. Timetable for the production of a series of background papers as listed in the June 2007 report (Section 13, paragraph 2)**

- RNA-based technologies for the treatment and control of animal diseases: target date is end of May 2008 (see discussion below, Lead Dr Whitelaw);
- Transgenic animal technology for livestock and horses (see Agenda Item 8): target date is September 2008 (Lead Dr Harpreet Kochhar);
- Reverse genetics as a new vaccine platform: target date November 2008 (Lead Dr Gay);
- Chimeric viruses for vaccine development; target date November 2008 (Lead Dr Gay).

The Group agreed that cDNA clones as a new vaccine delivery system and new vaccination schedules did not warrant a background papers at present.

#### **2.2. Timetable for the production of proposed background papers or *Terrestrial Manual* chapters, chapter sections or Appendices**

- Metagenomics as a diagnostic platform for detecting emerging and unknown pathogens: target date is November 2008 (Lead Dr Belak);
- New diagnostic technologies for surveillance and molecular epidemiology: target date June 2009 (Lead Dr Belak)

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2 IAEA: International Atomic Energy Agency

3 INRA: Institut national de la recherche agronomique

- Stem cell technologies: target date November 2008 (Lead Dr Whitelaw);
- Appendix for Part 3 of the *Terrestrial Animal Health Code (Terrestrial Code)*, which will be entitled “Animal Health Guideline for Transgenic Animals”: target date September 2008 (Lead Prof. Michel Thibier);
- A background awareness paper on transgenic animal technology for animals that are not covered by the document on transgenic animals in Section 2.1 (also see Agenda Item 8): target date is September 2008 (Lead Dr Eric Schoonejans).

### 2.3. Development of new chapters or additions for the *Terrestrial Manual* (Section 13, paragraph 3)

- Plasmid DNA vaccines (completed);
- Update the categories of biotechnology-derived vaccines in the sections relating to Chapter 1.1.7 Principles of veterinary vaccine production, including the release of biotechnology-derived products: target date November 2008 (Lead Dr Gay);
- DIVA vaccines and diagnostics: target date is end of January (Lead Dr Gay);
- A new chapter on the risk assessment of the release of biotechnology-derived vaccines: target date November 2009 (Lead Dr Schoonejans).

Proposed new chapters or additions

- Addition to Chapter 1.1.8. Biotechnology in the diagnosis of infectious diseases and vaccine development, entitled “Nanotechnologies in diagnosis and vaccine development” (to be new Section E, Leads Dr MacKenzie and Gay): target date is end of January 2008.

### 2.4. Position paper on RNA-based biotechnologies: potential future impact on animal health

Dr Whitelaw summarised the position paper he had prepared for the OIE. The following points were made:

- The impact of RNA-based biotechnologies is huge.
- As various forms of delivery of RNA products are identified, a wide range of applications becomes available.
- The delivery methods will have a tremendous impact on the classification of these products, for example whether they are delivered as drugs (e.g. RNA delivered in liposome or nanotechnology platforms) or through an expression system (e.g. a plant, plasmid DNA, transgenic strategy, etc.).
- The applications fall within two domains: 1) to control pathogens or their vectors and 2) to control a physiological or metabolic effect in an animal.
- In regard to pathogens, the application may include conserved sequences across different strains and therefore may allow the control of multiple pathogenic agents.
- The applications will be in the following order: 1) as a research tool; 2) to control pathogens; 3) to control an animal’s physiological process.
- At this point, regulatory jurisdictional issues cannot be determined until specific RNA-based products are defined. For instance, RNA-based biotechnologies may be regulated as a drug or a biological. The desired function, the application, or the delivery strategy may have an impact on the regulatory jurisdiction of these products.

- The use of this technology as a research tool is increasing exponentially and potential applications are innumerable.
- This technology has the potential to interface with nanotechnologies and transgenics.

The Group agreed that this field is still in its infancy and the development of specific guidance documents will have to wait for a specific product to be developed and its application defined. The use of RNA-based biotechnologies as an academic research tool does not require additional guidelines as this technology does not present new safety issues. The Group also agreed that general standards and points to consider for applications for pathogen control may require new or revised guidelines. As many RNA-based biotechnologies for pathogen control will most likely fit regulatory requirements for drugs, the Group recommends that the OIE *Terrestrial Manual* be amended to include drugs such as RNA-based biotechnologies products used as antivirals. RNA-based biotechnology applications will also include transgenics and the issues associated with these products should be addressed in the guidelines developed by the Group for transgenic animals.

The Group agreed to revise the RNA-based biotechnologies position paper to account of the above points and submit the paper to the Biological Standards Commission for further input and direction.

### **3. Report on the 7th Session of the Codex Ad Hoc Intergovernmental Task Force on Food Derived from Biotechnology**

Prof. Thibier was the representative of the OIE at this Task Force meeting in Chiba, Japan, and provided the Group with a report of the main outcomes of the meeting, as follows:

- Prof. Thibier complimented Dr Hiroshi Yoshikura, Chair of the Task Force, for his excellent leadership, which successfully produced a final report at the end of the meeting.
- Among the guidelines for adoption by the next Codex Commission was the Guideline for the Conduct of the Food Safety Assessment of Foods Derived from recombinant-DNA Animals, the adoption of which will lead to Step 5/8 of the Codex Proceedings (the guideline will be proposed at the next meeting with the recommendation to omit steps 6 and 7, i.e. the guideline is ready to be adopted as a Codex Standard). This guideline identifies the health status of the recombinant animal as one of the factors that is relevant to the safety assessment of recombinant-DNA animals. It was understood that the assessment of animal health status fell within the OIE mandate and was not covered by the Codex guideline.
- Prof. Thibier emphasised that after a long discussion by the Task Force (members act as representatives of their country and not as individual subject matter experts), the following footnotes were added to the guidelines:
  1. The guidelines were developed primarily for animals bearing heritable recombinant-DNA constructs.
  2. The food safety assessment of foods derived from animals bearing non-heritable constructs may require additional considerations.

Prof. Thibier communicated to the Group that the OIE has agreed to consider whether there are any issues related to food safety, animal health or welfare, in the case of animals treated with non-heritable DNA constructs (including recombinant vaccines). Experts from FAO<sup>4</sup> and WHO<sup>5</sup> should be invited to attend this discussion.

Dr Stuart A. Slorach, Chair of the OIE Working Group on Animal Production Food Safety, provided an extract of the report of the seventh meeting of the Working Group, held in Paris, 6–8 November 2007, Agenda Item 13, Biotechnology, as follows:

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4 FAO: Food and Agriculture Organization of the United Nations

5 WHO: World Health Organization



- At their meeting, the OIE Working Group reviewed the outcome of the Draft Guideline for the Conduct of the Food Safety Assessment of Foods Derived from recombinant-DNA Animals (described above by Prof. Thibier). Dr Slorach emphasised again that the assessment of animal health status fell within the OIE mandate.
- The Working Group noted the report of the 12–14 June 2007 meeting of the OIE *ad hoc* Group on Biotechnology and noted that the Group would next meet in Paris 27–0 November, 2007, and that the Group would address the recommendations of an FAO/WHO Expert Group on the status of foods derived from animals treated with recombinant DNA vaccines. As such, Dr Slorach accepted to be present at the meeting of the OIE *ad hoc* Group on Biotechnology and to report back to the Working Group.
- Dr Slorach provided a copy of the FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Recombinant-DNA Animals (Codex Document CX/FBT 07/7/3 Add.1, June 2007), which was held at the headquarters of WHO in Geneva, 26 February to 2 March 2007. The objective of the Expert Group was to provide scientific advice to FAO/WHO and their Member States on two sets of questions regarding: i) marker and reporter genes and ii) non-heritable applications. The Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology had specifically requested advice on these two questions.

The Group examined the summary FAO/WHO Joint Expert Consultation report, and Dr Gay noted that one of the recommendations for non-heritable applications was of particular concern as it questioned the food safety of animals administered recombinant-DNA vaccines. The recommendation states: “Given the complexity and importance of the animal health and food safety issues raised by recombinant-DNA vaccines, these issues should be considered by a joint FAO/WHO/OIE expert group.” The Group agreed that if WHO/FAO Joint Expert Consultation Group had the perception that recombinant-DNA vaccines may present animal health or food safety issues then these would of course need to be addressed. However, the Group expressed its reservation about presenting such an issue as fact when, in the case of recombinant-DNA vaccines, both science and over a decade of commercialisation has not revealed any safety issues associated with the use of recombinant-DNA vaccines, and stating the opposite sets an unnecessary precedent. In fact, recombinant-DNA vaccines have been the pillar upon which important infectious diseases of humans and livestock have been eradicated in regions of Europe and North America, e.g., rabies and Aujeszky’s disease (Pseudorabies).

The Group recommends that the section on non-heritable applications in the summary of the report of the FAO/WHO Expert Consultation on the Safety Assessment of Foods Derived from Recombinant-DNA Animals be submitted to the Biological Standards Commission and the Terrestrial Animal Health Standards Commission to obtain further direction. The section contains several recommendations directed to OIE for further action.

The Group recommends that organisations that need expert scientific advice such as WHO/FAO and the International Plant Protection Convention, consult the OIE on technical and scientific animal health issues.

#### **4. Follow-up of the recommendations by the *ad hoc* Group at October 2006 meeting on nanotechnologies and animal health**

The Group discussed the report on nanotechnologies submitted by Dr MacKenzie. The following points were made:

- Funding for nanotechnology research is expanding exponentially both in the private sector and in the public sector in the United States, Japan, the People’s Republic of China, and the European Union.
- The OIE appears to be ahead of the Codex Alimentarius in the consideration of these technologies. WHO/FAO have declared that they will initiate expert consultations on nanotechnologies. It is important that OIE decide how considerations of nanotechnologies will be coordinated with WHO/FAO.

- The field of nanotechnology is expanding significantly in human medicine and is bound to impact veterinary medicine – “nanoveterinary medicine”.
- Several branches have emerged from nanotechnology, such as nanomedicine, nanotoxicology, nanopharmacology, etc.
- The biggest stumbling block in progressing nanotechnologies are safety considerations. There is clear evidence of toxicology, such as crossing the blood–brain barrier. Therefore, the scientific community should work very hard to ensure that societal concerns do not impact this very promising field the way it did with animal biotechnology.
- One of the objectives of the OIE Publications Department is to share technical documents on nanotechnology to ensure that OIE Members are made aware of the fast evolution of this scientific field.
- The Group agreed that it was critical that nanotechnology be clearly defined to avoid confusion or overlap with existing technologies, such as products of biotechnology. The vast majority of scientific papers describe carbon-based molecules for the delivery of drugs. To avoid overlap, the focus should therefore be on the delivery system (i.e. the nanotechnology) and not on the drug or biological that is delivered.

The Group agreed that the focus of OIE should be on:

1. Terminology;
2. The methods of delivery;
3. Expected impact of nanotechnology in veterinary medicine and animal welfare include:
  - Diagnosis – i.e. injection of quantum dots;
  - Traceability – i.e. nanobarcodes;
  - Treatment of diseases – i.e. use of nanoparticles to deliver drugs (smart delivery systems);
  - New potential hazards related to nanotechnology;
  - Food safety.

This work should be progressed while taking into consideration work under way in other standard-setting organisations.

The Group agreed to revise the position paper based on input received during the meeting and submit the paper to the Biological Standards Commission for further input and direction (Lead Dr MacKenzie). The Group recommends that OIE work on:

1. Enhanced risk assessment methodologies for nanotechnologies;
  2. Pre-emptive animal health risk assessments of emerging nanotechnologies;
  3. Communication on nanotechnologies, including the benefits and risks;
  4. OIE coordinate its activities with WHO/FAO in the area of nanotechnologies;
  5. OIE should co-sponsor with WHO/FAO the upcoming expert consultation on nanotechnologies in 2008;
  6. A series of questions focusing on the role of nanotechnologies in animal health, animal welfare, and food safety should be prepared by OIE for the expert consultation’s consideration (several questions raised by the paper could serve as a starting point).
- 5. Identification and tracing of animals and animal products that have resulted from biotechnological intervention – Cooperation with the OIE *ad hoc* Group on Traceability**

The Group nominated Dr Kochhar to participate in the next meeting of the OIE *ad hoc* Group on Traceability.

## 6. Follow-up from the International Symposium 'Animal Genomics for Animal Health'

Dr Gay reported to the Group on the outcomes of the International Symposium on Animal Genomics for Animal Health with the following key points:

- The symposium exceeded the expectations of the Organising Committee with 260 scientists from 35 countries attending the 3-day event, which took place at the OIE headquarters from 23 to 25 October, 2007.
- The symposium provided an excellent opportunity for presentations of the latest data relating to genomics and animal health.
- The community representing animal health geneticists working on animal diseases was well represented and a wide variety of presentations were given, including an excellent overview of current and emerging techniques.
- There are challenges in engaging the animal health community in animal genomics research and although the symposium could have been better attended by animal health experts, a fair number of senior scientists attended. Noticeably absent from the symposium were a number of senior scientists from European veterinary schools and animal health research institutes.
- A successful roundtable discussion was organised, which highlighted the need for large international projects. These projects will need to be extensive to achieve critical mass and scale to make meaningful progress.
- A significant number of opportunities were identified, as follows:
  1. New research tools:
    - Genetic marker (marker-assisted selection, whole genome selection);
    - Transcript profiling (transcriptomics);
    - Proteomics.
  2. Applications:
    - Microbial genomics;
    - Understanding mechanisms of pathogen immune evasion;
    - Understanding innate and adaptive immunity;
    - Molecular mechanisms of host–pathogen interaction;
    - Selection of animals with desirable health traits (good responders to vaccination, genetic disease resistance).
  3. New tools to develop veterinary medicines:
    - Vaccines;
    - Antivirals;
    - Biotherapeutics.
- A questionnaire was distributed during the meeting to assess problems, solutions, and the next steps on four overarching issues:
  1. Quantitative population genetic studies to identify markers of health traits.
  2. Functional genomics of host-pathogen interactions.
  3. Translating genomic information to tools for controlling diseases.
  4. Integrating stakeholders support to advance animal genomics in animal health.

- The results of the roundtable discussion together with the input from the questionnaire will be used to build a ‘roadmap’ for the way forward, which will be included in the symposium proceedings.

The Group endorsed the development of such a ‘roadmap’. The proceeding will be published in the IABs<sup>6</sup> Karger series. The target date for publication is April 2008. As follow up, the Group recommends that a Second International Symposium on Animal Genomics for Animal Health be organised to review the progress made with the roadmap and to facilitate future progress. The Group recommends that the OIE facilitates the development of the ‘roadmap’ and the organisation of the next series of symposia.

## 7. Follow-up from the 8th OIE/WAVLD on Biotechnology

Dr François Diaz, OIE, reported on the recent WAVLD<sup>7</sup> conference in Melbourne, Australia. In response to discussion on the conference, Dr Diaz agreed to review any recommendations included in the conference proceedings and to inform the Group of any issues that it should consider.

## 8. Discussion of the Group on the preparation of an Appendix in Part 3 of the *Terrestrial Code*, which will be titled “Animal Health Guideline for Transgenic Animals” (see 2.2 above and Appendix III)

Prof. Thibier reported on the various intergovernmental organisations currently working on guidelines for the risk analysis of new reproductive biotechnologies. The table by Prof. Thibier and Dr Kochhar summarises the planned documents for addressing safety issues relevant to animal health and food safety of new reproductive biotechnologies (see [Appendix III](#)).

## 9. Format for Guidelines in the OIE Terrestrial Animal Health Code

Dr. Yamato Atagi, Project Manager, International Trade Department, OIE, provided for the Group an outline for writing Guidelines in the *Terrestrial Code*. Although there are some variations and not all elements appear accordingly, general format are as follows:

- Preamble (very rare)
- Introduction
- Purposes/Scope/Objectives
- Definitions
- Principles
- Recommendations

## 10. Future work programme/schedule

To be determined by the OIE. The next meeting is recommended for October 2008.

## 11. Other issues

The Group recommends that the OIE attend the next meeting of the Parties to the Biosafety Protocol to be held in Germany, 12–16 May 2008. That meeting will address issues that fall within the competencies of the OIE, such as animal health issues related to transgenic animals and recombinant-DNA pharmaceuticals for use in animals and the associated risk assessment to animals. The Group also recommends that the OIE provide, as appropriate, technical information on these issues and raise awareness of the work undertaken by the *ad hoc* Group on Biotechnology.

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.../Appendices

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6 IABs: International Association for Biologicals

7 WAVLD: World Association of Veterinary Laboratory Diagnosticians

**MEETING OF THE OIE AD HOC GROUP ON BIOTECHNOLOGY**  
**Paris, 28–30 November 2007**

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**Agenda**

1. Designation of rapporteur
  2. Review of the Terms of Reference: Proposals from Prof. Steve Edwards
    - 2.1. Timetable for the production of a series of background papers as listed in the June 2007 report (Section 13, paragraph 2)
    - 2.2. Development of new chapters for the *Terrestrial Manual* (Section 13, paragraph 3)
    - 2.3. Position paper on RNA-based biotechnologies: potential future impact on animal health, Bruce Whitelaw
  3. Report on the meeting of Codex Ad Hoc Intergovernmental Task Force on Food Derived from Biotechnology (to be discussed 29 November, when Dr Slorach can attend)
  4. Follow-up of the recommendations by the *ad hoc* Group at October 2006 meeting on nanotechnology and animal health (Anne Mackenzie to brief the Group)
  5. Identification and tracing of animals and animal products that have resulted from biotechnological intervention - Cooperation with *ad hoc* Group on Traceability
  6. Follow-up from the International Symposium ‘Animal Genomics for Animal Health’
  7. Follow-up from the 8<sup>th</sup> OIE/WAVLD Seminar on Biotechnology
  8. Discussion of the Group on the preparation of an Appendix in the part 3 of the Terrestrial Code which will be titled “Animal Health Guideline for Transgenic Animals”.
  9. Format for Guidelines in the OIE Terrestrial Animal Health Code
  10. Future work programme/schedule
  11. Other issues/ Finalisation of the draft meeting report
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Appendix II

**MEETING OF THE OIE AD HOC GROUP ON BIOTECHNOLOGY**

**Paris, 28–30 November 2007**

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**Table: Guideline for the risk analysis of new reproductive biotechnologies**

Technology	Health for living animals	Food safety	
		Heritable cDNA	Non-Heritable cDNA
<b>Cloning</b>	OIE <i>ad hoc</i> Group on Biotechnology June 2007	In progress IETS <sup>8</sup> January 2008	<b>NOT APPLICABLE</b>
<b>Transgenic animals</b>	Proposed guidelines OIE <i>ad hoc</i> Group on Biotechnology September 2008	Codex Ad Hoc Task Force, Chiba (Japan) September 2007	<i>Ad hoc</i> Group planned with OIE, FAO/WHO 2008

Prof. Thibier outlined the following key points:

- For animal health guidelines, the OIE *ad hoc* Group is completing the needed guidelines for transgenic animals.
- For food safety guidelines and cloning, there is no IGO<sup>9</sup> that is currently addressing this issue. The OIE needs to determine where the IETS guidelines are most appropriately located.
- In the Codex *ad hoc* IGO Task Force report, the OIE has committed to convene a meeting with WHO/FAO to address issues related to animals with non-heritable recombinant-DNA constructs, including recombinant-DNA vaccines. The Group recommends that OIE specify who will organise this meeting and the Terms of Reference for this meeting.

The Group considers that the inclusion of non-heritable cDNA as a food safety issue is not appropriate in what the Codex considers a GMO<sup>10</sup> or recombinant-DNA vaccine, as there is no cDNA delivered to the animal. In contrast, when the gene coding for the antigen is delivered to the animal (so-called DNA vaccines or live recombinant-DNA vaccines), this implies the somatic delivery of nucleic acid to the animal and therefore can be considered as a somatic gene modification. In this context, the genetic material is not heritable and can, in principle, be administered to animals in general, including cloned or transgenic animals.

The Group charged a Sub-Group with the preparation of an outline of the proposed guidelines for transgenic animals to be chaired by Prof. Thibier (see Table above):

Prof. Thibier provided an outline of the process for preparing the proposed *ad hoc* Group on Biotechnology guidelines for transgenic animals:

- The Sub-Group agreed to generate a draft outline during this meeting, 29 November 2007;
- Submit draft outline to IETS for input by January 2008;
- Prepare first draft guidelines by September 2008.

8 IETS: International Embryo Transfer Society

9 IGO: intergovernmental organisation

10 GMO : Genetically modified organism

The Sub-Group discussed the following points:

- The background paper on transgenic animal technology (see 2.1 above) will include production livestock (bovine, ovine, caprine, porcine) and horses (equine). The purpose of this paper is to provide a more comprehensive synthesis of issues related to transgenics that will not be included in the Appendix prepared for the *Terrestrial Code*.
- Recognising that additional animal species need to be considered, Dr Schoonejans proposed to write a separate background paper on animal species not covered above, to raise awareness of this area (see 2.2 above).
- The Sub-Group agreed that the outline/sections of the Appendix will follow the same general outline used for the Guidelines for Somatic Cell Nuclear Transfer in Production Livestock and Horses, completed June 2007:

**Section I:**

1. Overview – Risk needs to be assessed on a case-by-case basis
2. Scope – What is included and exceptions
  - a. Included
    - i. Release of transgenic animals
    - ii. Individual animal health concerns
    - iii. Herd health concerns
  - b. Exceptions
    - i. Ethical moral and socioeconomic effects
    - ii. Animal welfare
    - iii. Use of animal products such as cells, serum, blood, tissues, etc.
3. Definitions
4. Diagram

**Section II:** Risk analysis – general principles

**Section III:** Managing animal health risks associated with embryos

1. Oocytes
2. Sperm (if applicable)
3. Donor cells
4. Transgenic procedures

**Section IV:** Managing animal health risks related to the recipients (surrogate dams)

1. Animal health risk to the surrogate dam
2. Animal health risks posed by the surrogate dam to the transgenic embryo

**Section V:** Managing animal health risks of transgenic animals

**Section VI:** Managing animal health risks related to transgenic offspring

**Section VII:** Managing animal health risks associated with transgenic offspring derived from sperm or oocytes from transgenic animals (multiple transgenes)

**Section VIII:** The release of transgenic animals

1. The need for a risk assessment such as possible herd effect on susceptibility of disease

Prof. Thibier reported the outline of the guideline to the Group. The Group recommends its implementation.



**Draft text on Nanotechnologies proposed for inclusion in chapter 1.1.8 Biotechnology in the diagnosis of infectious diseases and vaccine development of the OIE *Terrestrial Manual***

## **E. NANOTECHNOLOGIES IN DIAGNOSIS AND VACCINE DEVELOPMENT**

Nanotechnologies involve working at the atomic, molecular and supra-molecular levels in the length scale of 1–100 nm range, in order to understand, create and use materials, devices and systems with fundamentally new properties and functions because of their small structure. The potential use of nanotechnologies in relation to animal health is currently being examined (8).

### **1. Disease diagnosis**

Nanotechnology is being considered of great use for medical diagnosis (3). Nanoparticles have exhibited tremendous potential for detecting disease markers, pre-cancerous cells and fragments of viruses. Also, metal coatings and metal nanoparticles functionalised with different biomolecules have been found useful in detecting specific proteins and antibodies. For example, researchers have synthesised a specially charged silicon nano-wire connected with an antibody receptor that can detect the presence of cancer markers in the blood even if the concentration of these antigens in blood is about a hundred-billionth of the protein content. These sensors are much more accurate than currently available technologies.

Also, in disease diagnosis, devices are being reported that resemble a glass microscope slide with tiny nanoscale imbedded pores that allow the device to examine DNA molecules in the blood for signs of disease (4).

New studies (1) have shown that ultra sound waves sense nanoparticles and the nanoparticles can brighten the resulting image. These bright spots may indicate that a few cells in an area may be on the verge of mutating and growing out of control. There is the suggestion that by combining ultrasound and nanotechnology definitive diagnoses may be reached without using invasive procedures such as biopsies.

Nanoparticles Diagnostics is running a suit of projects focussing on the development of rapid, portable diagnostic tests in animal and human health (5).

### **2. Vaccine development**

The majority of nanotechnology based applications relating to vaccines are focussed on enhancing vaccine delivery and effectiveness. For example, a nanoemulsion (2) has been developed consisting of very tiny droplets of oil suspended in water and stabilised by detergents. The droplets in the nanoemulsion are surface active and react specifically with the outer membrane of infectious organisms. The technology works differently than antibiotics or traditional antiseptics, and is safe for humans, animals and the environment. In the vaccine work, the mixture of nanoemulsion and either whole virus or protein is applied directly to the nose of animals. This presents the immune system components required to create a vaccine.

It is speculated that there is great promise for vaccines based on this technology because they can be administered without the use of needles or refrigeration and this would have particular appeal to developing countries.

In a specific application (7) scientists were able to trigger a strong immune response by treating the inside of animal's noses with a nanoemulsion and a recombinant protein of *Bacillus anthracis*. The animals developed several types of immune response after only two administrations. On the challenge, all the immunised animals survived, whereas none of the control animals did.

Further projects (6) are underway in regards to TransDermal delivery using patches structured on the skin side with microprotrusions which hold the drugs to be delivered. The protrusion face of the patch is applied to the skin where the protrusions cross the outer surface layer of the skin only reaching as far as the interstitial space and avoiding nerves and blood vessels. In this interstitial space, the nano-structured compounds are released from the surface of the protrusions and taken up by the cells of the immune system for vaccination applications. The patches are intended for applications in human and animal health for delivering vaccines, proteins and peptides, peptide hormones and other drugs.

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## **EXPERT SURVEILLANCE PANEL ON EQUINE INFLUENZA VACCINES**

**Mill Hill London (United Kingdom), 18 January 2008**

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### **Conclusions and recommendations**

#### **Influenza activity January 2006–January 2007**

2007 was a highly significant year for the epidemiology of equine influenza. Major epizootics of the H3N8 subtype occurred in Japan and Australia. In addition, reports to the International Collating Centre of the International Thoroughbred Breeder and Promed have described widespread influenza in Sweden, China, Mongolia, and Kazakhstan.

The outbreak in Japan affecting around 2000 horses was the first incursion since 1971 and was initially diagnosed in race horses in August. The outbreak in Australia affecting around 75,000 horses to date was first recognised among imported stallions in a quarantine station in late August, but at the time of diagnosis infection had already escaped into the recreational horse population. Outbreaks described in Mongolia and China occurred between October and November and were reported to have affected more than 50,000 horses. There were also numerous small outbreaks in Europe and the USA.

The viruses isolated in Japan and Australia were genetically closely related to A/eq/South Africa/03 and A/eq/Wisconsin /03, that were recommended in 2004 as the new prototype American lineage viruses for updating vaccines. At the time of the Japanese and Australian outbreaks, there were no commercially available vaccines containing A/eq/South Africa/03-like viruses.

There was clear evidence that thoroughbred horses involved in the Japanese outbreak and stallions in the Australian quarantine station, as well horses involved in outbreaks in Europe and the USA, succumbed to infection despite regular and in some cases recent vaccination. In some cases infection with substantial virus shedding occurred in the absence of clinical signs.

The Expert Surveillance Panel strongly urges vaccine manufacturers and licensing authorities to adopt the recommendations for updating vaccine strains for the American lineage viruses and facilitate their rapid licensing.

#### **Criteria applied to data submitted to assess the significance of antigenic drift for vaccine efficacy**

For the 2007 review of equine influenza, data on virus isolates from Australia, Japan, Ireland, the USA and UK were considered. No viruses were received from other reported outbreaks.

As part of the review of data submitted, the panel re-examined the criteria used for assessing antigenic variation and its potential significance for vaccine efficacy.

It was agreed that:-

Breakdown of vaccines containing earlier strains in the face of field infection with new strains despite up-to-date vaccination is an important criterion for significance of antigenic drift. The data are considerably strengthened when infection is verified in horses with high levels of vaccinal antibody in acute phase sera (Newton *et al.*, 1999) rather than relying on records of recent vaccination, as some animals respond poorly to vaccination. In 2007 such data were available from Japan, Australia, UK and USA.

Discrimination of viruses using haemagglutination inhibition (HI) tests with ferret antisera was currently the most reliable method of assessing antigenic relationships between viruses, particularly when these antigenic distances are depicted using antigenic cartography (Smith *et al.*, 2004). All viruses isolated in 2007 were characterised as American lineage viruses in HI tests.

Discrimination between viruses in HI tests using post-vaccination field sera has been abandoned as equine sera from repeatedly vaccinated horses is highly cross reactive.

Attempts to measure cross protection between strains in a hamster model (Daly *et al.*, 2004) have also been abandoned as some equine viruses fail to replicate adequately in the hamster.

While it was recognised that cross protection studies in horses are the gold standard (Mumford, 1999), the need to use large numbers of horses to gain statistically significant results and the lack of availability of seronegative animals at certain times of the year precludes this approach as a feasible criterion.

To date antigenic relationships measured by HI using ferret antisera have correlated with the outcome of cross protection studies in horses (Mumford, 1999) and field observations (Newton *et al.*, 1999).

Sequencing of the HA1 gene provides useful supporting data on genetic relationships between isolates.

Work is ongoing to compare the discriminatory power of horse antisera with ferret antisera in HI tests.

### **Nomenclature of H3N8 strains**

Since the divergence of the HAs of H3N8 subtype viruses into American and Eurasian lineages, which occurred around 1989, this virus has continued to evolve into a number of sublineages or “clades”.

Lai *et al.* (2001) described three sublineages of the American-like viruses, which were designated Argentina, Kentucky and Florida with the Kentucky lineage being the most prevalent group of viruses during the 1990s. The evolution of the Florida sublineage resulted in the appearance of variant viruses, represented by A/eq/South Africa/03, which could be distinguished antigenically from the original American lineage prototype viruses (A/eq/Newmarket1/93, A/eq/Kentucky/94) and this observation instigated the 2004 recommendations to update the American lineage virus vaccine component to an A/eq/South Africa/03-like virus. Within this sublineage, two groups of viruses with divergent HAs have been recognised, which for the sake of clarity are provisionally referred to as clades 1 and 2. Clade 1 includes viruses such as A/eq/South Africa/03 A/eq/Ibaraki/07 and A/eq/Sydney/07. Clade 2 is represented by A/eq/Newmarket/03. Clade 1 viruses have been isolated predominantly in the USA, Japan and Australia. Clade 2 viruses have been isolated in Europe. Their further evolution and relative prevalence is being monitored. Assessment of potential antigenic differences awaits the production of new reagents.

No European Lineage viruses were isolated in 2007. Thus, since 2003 when widespread infection by A/eq/South Africa/03-like and Newmarket/03-like viruses occurred, very few European lineage viruses have been recovered.

Laboratories that isolate viruses are urged to submit them to OIE or WHO Reference Laboratories or other specialist laboratories for further analysis to enable current prevalence of the different variants to be assessed.

### **Vaccines**

Many vaccines still contain American lineage viruses such as Kentucky/94 and Newmarket/1/93, which were first recommended over 10 years ago. However, because of the practice of some vaccine manufacturers of updating strains on an *ad hoc* basis, other viruses such as A/eq/Kentucky/97, A/eq/Kentucky/98, and A/eq/Kentucky/2002 have also been used. At the time of writing no vaccine containing an A/eq/South Africa/03-like virus is available although it is understood that one vaccine manufacturer has updated and is currently completing the licensing process.

**The 2008 recommendations for equine influenza vaccine strains are as follows:-**

There is no requirement for inclusion of an H7N7 virus.

Manufacturers should adopt the 2004 recommendations and update the American lineage H3N8 component of their vaccines to an A/eq/South Africa/03-like virus. Other viruses such as A/eq/Wisconsin/03, A/eq/Ohio/03, A/eq/Ibaraki/07 and A/eq/Sydney/07 are also suitable.

There is no requirement to update the European lineage H3N8 virus component. Current strains in use are A/eq/Suffolk/89, A/eq/Newmarket2/93, A/eq/Borlange/91. If companies are considering including European viruses they should consult with experts to establish the current situation and availability of recent isolates.

**Standard Reagents**

Reference reagents specific for the recommended European lineage vaccine strains are available for standardisation of vaccine content by Single Radial Diffusion (SRD) assay and can be obtained from the National Institute of Biological Standards and Control (NIBSC) email: [enquiries@nibsc.co.uk](mailto:enquiries@nibsc.co.uk). Preparation of reagents for A/eq/South Africa/03-like viruses is under review.

Four equine influenza horse antisera against A/eq/Newmarket/77(H7N7), A/eq/Newmarket/1/93(H3N8), A/eq/Newmarket2/(H3N8) and A/eq/South Africa/03(H3N8) are available as European Pharmacopoeia Biological Reference Preparations for serological testing of vaccine responses using the single radial haemolysis test. Sera may be sourced from EDQM <http://www.pheur.org>.

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