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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

***AD HOC* CODEX INTERGOVERNMENTAL TASK FORCE ON ANTIMICROBIAL RESISTANCE**

First Session

Seoul, Republic of Korea, 23-26 October 2007

REVIEW OF THE WORK BY FAO, WHO AND OIE ON ANTIMICROBIAL RESISTANCE

(prepared by FAO, OIE and WHO)

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

Background

1. The use of antimicrobials for treatment and prevention of diseases in food production animals contributes to the protection of animal health and welfare. The potential risk of emergence and spread of resistant microorganisms associated with such use has been addressed during the last decade by the international organisations, WHO, OIE and FAO, included in this review. In particular, the fact that to a large extent the same classes of antimicrobials are used both in humans and animals, and few new antibiotics from existing classes and new classes have been developed to replace those that have become relatively ineffective through resistance, has led to an agreement on the necessity to develop measures such as prudent use of antimicrobials and surveillance of emerging antimicrobial resistance in both the human and the veterinary sectors. As far as veterinary sector is concerned, food is to date considered the most important vector for spread of resistance between animals and humans.

WHO Activities for Containment of Foodborne Antimicrobial Resistance

2. WHO's involvement with the issue of foodborne antimicrobial resistance dates back to 1997, when medical problems arising from the use of antimicrobials in livestock production were identified and concern was raised that drug-resistant pathogens could be transmitted to humans via the food chain (WHO/EMC/ZOO/97.4, http://www.who.int/emc/diseases/zoo/antimicrobial.html).

3. Following concerns raised by the use of quinolones in food animals and emergence of quinolone-resistant enteric bacteria, a WHO consultation was held in June 1998 in Geneva to address the issue (WHO/EMC/ZDI/98.12).

4. Concern that extensive use of antibiotics in animal food production may further accelerate the development of antimicrobial resistance, led the World Health Assembly to adopt in 1998 a resolution (WHA51.17) on antimicrobial resistance urging member states to encourage the reduced and rationale use of antimicrobials in food-animal production. This resolution was followed by the development in 2000 of WHO Global principles for the containment of antimicrobial resistance in animals intended for food (http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm). The WHO Global Principles provides a framework of recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of human health. The Global principles are part of a comprehensive WHO Global Strategy for Containment of Antimicrobial Resistance.

5. WHO's Global Strategy for Containment of Antimicrobial Resistance was published in 2001 (http://www.who.int/drugresistance). A multi-sectoral approach to the problem was recommended, main recommendation being to establish national task forces to coordinate interventions aimed at:

- strengthening surveillance of use and resistance
- improving use of antimicrobial drugs
- improving access to appropriate antimicrobials
- reducing the disease burden and spread of infection
- enforcing regulation and legislation related to containing antimicrobial resistance
- developing appropriate new drugs and vaccines

6. In 2002, WHO issued reports on the monitoring of antimicrobial usage (*Monitoring Antimicrobial Usage in Food Animals for the Protection of Human Health*, Report of a WHO Consultation, Oslo, Norway, 10-13 September 2001, http://www.who.int/emc/diseases/zoo/antimicrobial.html) and on the impact of termination of use of antimicrobials as growth promoters (*Impact of Antimicrobial Growth Promoter Termination in Denmark/ The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark*, Foulum, Denmark, 6-7 November 2002, http://www.who.int/salmsurv/links/gssamrgrowthreportstory/en).

CRITICALLY IMPORTANT ANTIMICROBIALS

7. The WHO organized a working group consultation in 2005 in Canberra, Australia and issued a list of Critically Important Antibacterial Agents (CIAA) for Human Medicine. The experts categorized antimicrobial drugs as *critically important*, *highly important* and *important* based on two criteria. The WHO list of Critically Important Antimicrobials was reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicine in March 2007.

8. A second WHO Expert meeting on critically important antimicrobials was held in May 2007 in Copenhagen, Denmark to update the list as recommended in Canberra, taking into account recent development on antimicrobial resistance and recommendations from the WHO Expert Committee on the Selection and Use of Essential Medicine. In addition WHO also asked the experts to prioritize within the critically important category, in order to allow allocation of resources on the agents for which management of the risks from antimicrobial resistance are needed most urgently. This prioritization resulted in the designation of quinolones, 3rd/4th generation cephalosporins and macrolides as being the three classes to be considered in priority.

9. The development of WHO list should be followed by proposals of strategies for the specific limitation use of CIAA in animals in order to prevent/contain resistance to those antimicrobials.

OIE Activities for Containment of Foodborne Antimicrobial Resistance

10. Since 1997, due to the growing importance of antimicrobial resistance at a world-wide level, the OIE requested its Collaborating Centre for Veterinary Medicinal Products, in Fougères, France, to implement an action plan in this field. After a wide exchange of view and assessment of the challenges, the International Committee of OIE decided to create an ad hoc group of internationally recognised experts on antimicrobial resistance and to define the mandate and terms of reference to be followed by this Group.

11. The first milestone was to issue five guidelines:

- Guidelines for the harmonisation of antimicrobial resistance surveillance and monitoring programmes
- Guidelines for the monitoring of the quantities of antimicrobials used in animal husbandry
- Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine
- Laboratory methodologies for bacterial antimicrobial susceptibility testing
- Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals

12. These guidelines were adopted respectively by the OIE General Session of the OIE in May 2003 for the four first mentioned and in 2004 for the fifth one. Through this adoption, the guidelines became OIE international standards.

13. A continuous follow up is performed by the OIE *ad hoc* group on antimicrobial resistance enabling whenever needed their update. In particular Appendix 3.9.4 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. This revised guideline was adopted the May 2005 OIE General Session.

CRITICALLY IMPORTANT ANTIMICROBIALS

14. Following the two Expert Workshops on Non-Human Antimicrobial Usage organised by FAO, OIE and WHO, two main ideas emerged: the concept of 'critically important antimicrobials' and the establishment of a task force on antimicrobials resistance.

15. The concept of 'critically important' classes of antimicrobials for human and animal usage should be developed by WHO and OIE, respectively. The list of Critically Important Antibacterial Agents for Human Medicine is mentioned in point 2 of this paper. In January 2005, the OIE *ad hoc* group proposed to define and designate Veterinary Critically Important Antimicrobials (VCIA). This concept was endorsed by the OIE Biological Standards Commission and adopted by the OIE International Committee during the 73rd General Session in May 2005. The OIE referred the task of establishing a list of VCIA to the Ad hoc Group on Antimicrobial Resistance. The OIE *ad hoc* group prepared a questionnaire to collect proposals on VCIA as well as comments regarding the definition and aim of the list. The questionnaire was sent to the then 167 OIE Member Countries and to International Organisations with a co-operation agreement with the OIE in order to establish a list of VCIA. Information to justify the inclusion of these antimicrobials was also requested. The results were collated by the OIE Collaborating Centre for Veterinary Medicinal Products and presented to the *ad hoc* group.

16. In the view to develop a list of critically important antimicrobials for veterinary medicine, the *ad hoc* group reviewed in January 2006 the data provided in the analysis based on the information supplied by OIE Member Countries. A general agreement was expressed by respondents on the criteria proposed by OIE and a list of proposed VCIA was compiled. The report and the executive summary were endorsed by the Biological Standards Commission and were submitted for adoption by the OIE International Committee during the General Session in May 2006. The General session, asked the OIE ad hoc group on antimicrobial resistance to refine the list and to consider breaking it down into subcategories according to type of usage. The ad hoc group met in September 2006 and suggested a new list, which was adopted in May 2007, during the 75th General Session of the OIE International Committee.

.FAO Activities for Containment of Food-borne Antimicrobial Resistance

17. FAO's involvement with the issue of food-borne antimicrobial resistance include normative and field activities, an are carried out for several units, mainly the Nutrition and Consumer Protection Division (AGN), the FAO's Fishery Industries Division (FII)and the Animal Production and Health Division (AGA). The activities consider the food chain approach and are focus on prevention. Some of the normative activities have been carried out jointly with WHO.

18. AGN provides the FAO part of the Secretariat for the Joint FAO/WHO Expert Committee on Food Additives (JECFA) which, since 1956 has continually developed principles for safety assessment of chemicals in food. In 1996 JECFA began the assessment of antimicrobial drug residues at its 47th session. This assessment includes the safety of the residue profile of veterinary drugs and proposes maximum residue limits levels compatible with ADI. The decision tree for the establishment of the ADI includes consideration of the potential for the drug to develop antimicrobial resistance in human goat microflora and the mechanisms for resistance development. The JECFA guidance on the microbiological ADI was harmonised by the 66th session of JECFA with the guidance adopted by the Veterinary International Cooperation on Harmonization of technical requirements fro Registration of veterinary Medicinal Products (VICH GL36). The JECFA risk assessment framework for residues of antimicrobial veterinary drugs has been developed and are used on the international and national, regional level.

19. FAO/WHO/RIVIM organizes in November 2005 and international workshop on Updating the principles and Methods of Risk Assessment : maximum, Residue Levels (MRLs) for pesticides and veterinary drugs within the framework of the Joint FAO/WHO project to Up date the principles and Methods for the Risk Assessment of Chemicals in Food launched in 2002.

20. In addition to this FAO has organised several meeting related to the impact of veterinary drug residues in food, for example the FAO/WHO technical workshop on residues of veterinary drug residues without ADI/MRLs held in Bangkok, Thailand in August 2004 which analysed the disruptions caused by the detection of chloramfenicol and nitrofurans in foods from animal origin, identified the scientific, technical and regulatory problems created by this findings and make recommendations to address the issue (http://www.fao.org/docrep/008/y5723e/y5723e00.htm).

21. In the fisheries sector, the Fish Utilization and Marketing Service of the FAO's Fishery Industries Division has recently up-date with 2006-2007 data, a Fisheries Technical Paper "Causes of detentions and rejections in international trade" (FTP No. 473) The document highlight the implications of misuse of antibiotics on international trade in fisheries and provides information on rejections/import refusals/rapid alerts in major importing countries/regions, USA, European Union, Japan and Canada. Details of number of cases, antibiotic involved, continent of origin of the product are provided. This information should be helpful to fish exporting countries to take measures to prevent such cases.

22. A number of training courses/workshops have been conducted in different regions. Those events covered the issue of antibiotic residues, its implication for international trade, risk assessment principles and application in the fisheries sector. Some examples are the courses undertaken through the TCP/3071/RAS in Asia involving eight countries; a workshop in Saragoza, Spain held in association with CIHEAM/IAMZ for countries from the Mediterranean region, Africa and Latin America.

23. A Workshop was conducted in Vietnam, where emphasis put on following the FAO Code of Conduct for responsible fisheries. The Guidelines for Responsible Fish Utilisation is at present being revised in consultation with user countries and clauses pertaining to Good Aquaculture practice, avoiding misuse of antibiotics have been added. These revisions were discussed with participants from ten Asians countries.

24. FAO co-sponsors the World Seafood Congress in 2007. The issue of antibiotic residues in fish in international trade will be discussed and FAO is supporting participation of developing countries in this event.

25. In addition to this FAO has provided scientific advice to the Codex Committee on Fish and Fishery Products to finalize the Code of Practice, including section 6 on intensive aquaculture. A comprehensive Guidance document for the application of Good aquaculture practice (GAP) and HACCP in other aquaculture systems (extensive, semi-extensive and integrated aquaculture; e.g. shrimp, carp and tilapia aquaculture) is in the final stages of its development and will be disseminated through the organization of two workshops in 2008, one in Asia and another one in Latin America.

26. At the request of its members, FAO is developing International guidelines for certification in aquaculture. Two meetings were held respectively in May in Bangkok, Thailand and in July – August 2007 in Fortaleza, Brazil to discuss content of the guidelines and a roadmap towards their development. These guidelines for certification in aquaculture will address food safety/quality, animal health and welfare, as well as social and environmental aspects.

27. A study is being conducted on the private standards and certification schemes being implemented in world fish trade, and their implications for exporting developing countries, in particular in relation to the provisions of the SPS/TBT agreement.

28. In the area of food production animals, AGA has produced several guidance documents on Good Agriculture Practices for the Meat and Livestock Sector; Good Practices for the Poultry Sector; Good practices for the Milk Sector and has carried out several meetings and workshops worldwide to discuss their application. Whiting the FAO Animal production and health series, AGA has issued the publication No. 160 on non-human antimicrobial usage and antimicrobial resistance: management options, and the publication No. 162 on antibiotic growth promoters in food animals, which contain useful recommendations to the correct use of these products and are an important tools on the prevention of antimicrobial resistance derived from this use.

29. FAO staff has provided expertise and participated in WHO and OIE activities related to antimicrobial resistance mentioned in section 2 and 3.

Recent activities following the request for joint activities to address the issue of antimicrobial resistance by Codex

30. Considering that antimicrobial resistance is a multi-factorial problem that requires a multi-disciplinary and a multi-agency approach, the Executive Committee of the Codex Alimentarius Commissio (CAC) at its 53rd session in 2001 recommended that FAO, WHO and the OIE should consider addressing jointly all issues of non-human usage of antimicrobials and antimicrobial resistance. The three organizations were committed to undertake a joint effort on this matte rand therefore they initiated an joint consultative process on non-human usage of antimicrobials and antimicrobial resistance, in accordance with the CAC risk analysis principles.

31. The first step was to hold two workshops. The first one on scientific assessment was held in December 2003 in Geneva, and the second on management options was held in March 2004 in Oslo. The selection of experts was undertaken jointly by the three organizations following a well defined open and transparent procedure to ensure adequate expertise, balance and independence of the scientific advice.

32. The first workshop on Non-Human Antimicrobial Usage included a preliminary scientific assessment of all non-human uses of antimicrobials in animals and plants, and their role in antimicrobial resistance. Based on the available scientific information, the participants concluded that there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials, and the consequences of antimicrobial resistance are particularly severe when pathogens are resistant to antimicrobials critically important in human medicine.

33. The second workshop recommended the establishment of a Codex task force with the participation of the OIE to deal with the issue of antimicrobial resistance arising from non human use considered the broad range of possible risk management options for antimicrobial resistance from non-human use of antimicrobials. In particular, it focused on potential directions of future Codex, FAO, WHO and OIE work in this area, in order to prevent and minimise antimicrobial resistance at the global level. To ensure that the conclusions of the 2nd Workshop reflected the perspectives of interested parties, the major stakeholder groups (e.g. members of the pharmaceutical industry, farmers, food processors, consumers, regulatory agencies, and veterinarians) participated in the meeting. A second recommendation to develop the concept of Critically Important Antimicrobial Agents (CIAA) for humans is addressed in section 2.

34. A third joint expert meeting was held in June 2006 in Seoul, Republic of Korea, on antimicrobial use in aquaculture and antimicrobial resistance. All pertinent and scientific information collected over the last years on antimicrobial use in aquaculture and its consequences for public health was analyzed, using the complementary expertise of FAO, WHO and OIE. The overall objective of this meeting was to discuss and to outline strategies and recommendations to minimize the risk related to antimicrobial use in aquaculture and its consequences for human public health and animal health, based on scientific assessment. The reports from these meetings are available at http://www.who.int/foodborne_disease/resistance/en/ ; http://www.fao.org/ag/agn/agns/micro_antimicrobial_en.asp .

35. The outcome of all these activities should be considered in the elaboration of strategies to prevent/contain resistance to those antimicrobials, including possible specific limitations of their use in food production animals. An appropriate balance should be struck between animal health needs and human health consideration taking into account the different risk management approaches and the possible overlaps of the lists of critically important antibiotics prepared by WHO and OIE. In order to do so, FAO/OIE/WHO is organizing a joint FAO/OIE /WHO Expert Consultation on Critically Important Antimicrobials in Rome, Italy 26 - 30 November 2007 (http://www.fao.org/ag/agn/agns/micro_antimicrobial_en.asp). The objectives of the meeting are:

- To consider the two lists of critically important antimicrobials developed by WHO and OIE in order to:
  a) find an appropriate balance between animal health needs and public health considerations taking into account the overlap of the two lists;
  b) identify as feasible current and likely hazards to public health resulting from this overlap;
  c) identify the combination: human pathogen, antimicrobial, animal species, human use that could be considered by risk managers as priority for a complete risk assessment;
  d) review current management strategies and options for maintaining the efficacy of critically important antimicrobials for humans and animals;
  e) provide recommendations on future FAO, WHO and OIE activities.

36. The expert consultation will consider also the needs of scientific advice derived from the first session of the Codex task force on antimicrobial resistance.

37. Taking in consideration that this issue is of great importance for a number of stakeholders, the tree organizations jointly have organised a stakeholders meeting, immediately prior to this expert meeting, to allow representatives of these organizations to express their views on this important issue. The meeting will take place in FAO/HQ, Rome, Italy on 26 November 2007.

38. FAO/OIE/WHO pay particular attention to ensure that the expert consultation and other related meetings follows the principles agreed for the provision of scientific advice http://www.fao.org/ag/agn/agns/files/Final_Draft_EnglishFramework.pdf to ensure the scientific basis of the recommendations to be made at the meeting. Moreover, the three organizations stresses the fact that new work and future joint consultations should not duplicate the work done and still to be done by the Codex Task Force.

Codex *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance

39. This task force was established during the 29th session of the Codex Alimentarius Commisson, as a Codex *Ad Hoc* Intergovernmental Task Force on Antimicrobial resistance. The objectives, as defined in the terms of reference, is to provide guidance on how to assess the risks to human health associated with the presence in food and feed of resistance organism or resistance genes.

40. FAO/OIE/WHO supports this initiative and stresses the task force to consider in priority non-human use of antimicrobial agents that are used therapeutically or non- therapeutically in animals and that are critically important for human medicine and animal health.

41. In developing guidance on methodology and policies for risk assessment for antimicrobials used in human and veterinary medicine, it is recommended that the Codex Task Force does not duplicate already existing guidelines. The OIE considers that this work in Codex should be complementary to existing OIE standards.