

CONSULTATIONS AND WORKSHOPS

Antimicrobial Use in Aquaculture and Antimicrobial Resistance

**Report of a Joint FAO/OIE/WHO
Expert Consultation on Antimicrobial Use in
Aquaculture and Antimicrobial Resistance**

Seoul, Republic of Korea, 13–16 June 2006



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EXECUTIVE SUMMARY

It is well recognized that the issues of antimicrobial use in food animals are of global concern. International interdisciplinary cooperation is essential, and FAO, OIE and WHO have organized a number of consultations to address the issues related to antimicrobial use, the emergence of resistant pathogens and the potential public health impact. Previous consultations have judged that antimicrobial resistance is a problem related to all types of antimicrobial usages, including use in humans and animals. Antimicrobial resistance in human pathogens is largely the consequence of use in human medicine and terrestrial animal agriculture. While difficult to assess in aquaculture the relative risk to humans is likely to be lower. The previous consultations did not address thoroughly the use of antimicrobials in aquaculture and the public health impact of such use. FAO, OIE and WHO therefore organized the present consultation to evaluate the usage patterns, and public health impact of this use, and to develop strategies to minimize the risk.

Although data on quantities of antimicrobials used in aquaculture are not available in most countries, available evidence suggests that the amount of antimicrobials used in aquaculture in most developed countries is limited and in some countries the quantity has been decreasing. Nevertheless, large quantities of antimicrobials are used in aquaculture in some countries, often without professional consultation or supervision. Furthermore, an important proportion of aquatic animals raised for the global aquaculture industry are raised in countries with insufficient regulations and limited enforcement for the authorization of antimicrobial agents used in animals. In some countries availability of registered antimicrobials is insufficient which contributes to illegal use.

The public health hazards related to antimicrobial use in aquaculture include the development and spread of antimicrobial resistant bacteria and resistance genes, and the occurrence of antimicrobial residues in products of aquaculture. The greatest potential risk to public health associated with antimicrobial use in aquaculture is thought to be the development of a reservoir of transferable resistance genes in bacteria in aquatic environments from which such genes can be disseminated by horizontal gene transfer to other bacteria and ultimately reach human pathogens. However, a quantitative risk assessment on antimicrobial resistance in aquaculture is difficult to perform owing to lack of data and the many different and complex pathways of gene flow.

Prevention and control of bacterial diseases in aquatic animals is essential to minimize the use of antimicrobials and avoid the negative impact of antimicrobial resistance. Efficacious vaccines and improved systems for mass vaccination of finfish should be developed, and an optimization of vaccine licensing procedures should be promoted.

Programmes to monitor antimicrobial usage and antimicrobial resistance in bacteria from farm-raised aquatic animals and their environment should be implemented and national databases should be developed to achieve efficient communication.

A practical, feasible and cost-effective approach should be developed and implemented, building on the work of FAO, the Network of Aquaculture Centres in Asia-Pacific (NACA) and others to strengthen aquaculture extension support and technical advice and assistance to small-scale aquaculture to increase awareness, implement good aquaculture practices¹, and

¹ FAO is currently working on technical guidelines for the improvement of safety and quality in aquaculture, which will be field-tested in early 2007 and finalized the same year.

strengthen government and industry institutions for aquatic animal health. The strategies should be integrated within an overall approach for poverty alleviation with particular emphasis on access to credit (micro-credit) and to extension support services.

The *WHO Global Principles for Containment of Antimicrobial Resistance in Animals Intended for Food*, the *OIE International Standards on Antimicrobial Resistance*, the *Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005)* and the *Codex Code of Practice for Fish and Fishery Products (Section 6 - Aquaculture Production) (CAC/RCP 52-2003)* provide recommendations on the responsible and prudent use of antimicrobial agents in veterinary medicine to reduce the over-use and mis-use of antimicrobials in animals for the protection of human health. (Although aquaculture was not specifically considered when the WHO Principles, OIE Guidelines and the Codex Code of Practice (CAC/RCP 61-2005) were adopted, and the Codex Code of Practice for Fish and Fishery Products does not cover extensive fish-farming systems or integrated livestock and fish culture systems that dominate aquaculture production in the world, they also pertain to the use of antimicrobial agents in aquaculture. Antimicrobial agents used in aquaculture should therefore be used in accordance with the WHO Global Principles and with the relevant provisions of the OIE Terrestrial Animal Health Code and Codex texts made applicable to aquatic animals. Antimicrobial agents defined as “critically important for human medicine” by WHO will require special risk assessment and management in respect of non-human antimicrobial use.

The use of antimicrobials in aquaculture should be seen within a general framework for risk analysis of antimicrobial resistance in relation to the use of antimicrobials in animals.

The future *Codex Ad-Hoc* Intergovernmental Task Force on Antimicrobial Resistance with respect to Food Safety should work in close collaboration with OIE to develop risk analysis principles and risk assessment guidelines. Within this process a full risk assessment should be developed in priority areas

PREAMBLE

A Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance was held in Seoul, Republic of Korea, from 13 to 16 June 2006. The meeting was hosted by the Korean Food and Drug Administration and was attended by 25 experts from 19 countries (see Annex 1 - list of participants).

Following the delivery of opening remarks by Dr C. J. Moon, Commissioner, Korean Food and Drug Administration, and Dr Jørgen Schlundt, Director, Department of Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, a silence of one minute was observed in memory of the late Dr Lee Jong Wook, who had passed away suddenly in Geneva, Switzerland, on 22 May 2006, during his term of office as Director-General of the World Health Organization.

Dr Gun Jo Woo was elected as Chairman of the meeting, and Dr Herbert Schneider and Dr Peter Smith were elected as Vice-Chairman and Rapporteur respectively.

It was decided to address the main issues of concern in two working groups. Dr Hilde Kruse and Dr Iddy Karunasagar were elected as Chairman and Rapporteur of Working Group 1, which would be dealing with assessment of the risk; and Dr Fred Angulo and Dr Carl Uhland were elected as Chairman and Rapporteur of Working Group 2, which would be dealing with risk management options.

BACKGROUND

It is well recognized that the issues of antimicrobial use in food animal production are of global concern; international interdisciplinary cooperation is therefore essential. FAO, OIE and WHO have organized a number of consultations to address the issues related to antimicrobial use, the emergence of resistant pathogens and the potential public health impact. Considering that antimicrobial usage and resistance is a multifactoral problem, the Executive Committee of the Codex Alimentarius Commission, in its 53rd session, recommended that FAO, OIE and WHO should give consideration to convening a multidisciplinary expert consultation. All issues of antimicrobials in agriculture and veterinary use (including aquaculture) should be considered and the role played by antimicrobials as essential human and veterinary medicines should be taken into account.

Following this request from Codex, a consultative process on the non-human use of antimicrobials and antimicrobial resistance was initiated jointly by FAO, OIE and WHO, with a first workshop on risk assessment organized in Geneva, in December 2003, followed by a workshop on risk management options organized in Oslo, in March 2004. However, these workshops did not address thoroughly the use of antimicrobials in aquaculture and the public health impact of such use. The present consultation was therefore planned to fill this gap and complement this consultative process.

This expert consultation was jointly organized by FAO, OIE and WHO to present and discuss scientific findings, and to reach scientific consensus on issues regarding public health aspects of antibiotic resistance and antibiotic usage in aquaculture. It was recommended to use the risk analysis framework that had been promoted by the three organizations, as well as the Codex Alimentarius Commission, for more than a decade. The consultation analysed all pertinent and scientific information collected over the last years on antimicrobial use in aquaculture and its consequences for human public health, using the complementary expertise of FAO, OIE and WHO.

The goals of this consultation were to:

- assess the pattern of the use of antimicrobials in terms of quantities as well as in terms of classes of antimicrobials;
- identify current and potential future hazards to public health of antimicrobial usage in aquaculture;
- assess the risk associated with the use of antimicrobials in aquaculture using risk assessment methodologies currently available; and
- identify priorities/strategies for further work oriented to improve present risk management options in this field at national and international level (FAO/OIE/WHO).

In advance of the consultation, three drafting groups were asked to prepare background papers on aquaculture systems (under the supervision of FAO), on animal health issues (coordinated by the OIE) and on public health issues (coordinated by WHO). FAO contributed to fish safety issues as well.

Summaries of the three background papers prepared by the drafting groups are provided in Annex 3.

After presentation of the three background papers, the experts were divided in two working groups (see Annex 2 - Agenda).

- Working group 1 was asked to assess the public health risks associated with the use of antimicrobials.
- Working group 2 was asked to propose management options to reduce the risks associated with the use of antimicrobials in aquaculture.

On the basis of the background papers, discussions during the working group sessions, scientific literature, conclusions and recommendations from previous expert consultations and reports, the experts issued the recommendations presented in this report.

REPORT OF A JOINT FAO/OIE/WHO EXPERT CONSULTATION ON ANTIMICROBIAL USE IN AQUACULTURE AND ANTIMICROBIAL RESISTANCE

Seoul, Republic of Korea, 13-16 June 2006

PART I - ASSESSING THE RISK ON PUBLIC HEALTH OF THE USE OF ANTIMICROBIALS IN AQUACULTURE

Antimicrobial resistance represents an extremely complex area of microbiology, particularly because of the promiscuity of resistance genes, the importance of horizontal gene transfer and the many different and complex pathways of gene flow. It is therefore not possible to perform a quantitative risk assessment on antimicrobial resistance in aquaculture. Here we are assessing the risk using the common framework for risk assessment as laid down by the Codex Alimentarius Commission, while taking into account certain aspects mentioned in the OIE framework for risk assessment.

1. Hazard identification

The public health hazards related to antimicrobial use in aquaculture include the development and spread of antimicrobial resistant bacteria and resistance genes, and the occurrence of antimicrobial residues in products of aquaculture.

1.1. Antimicrobial resistance

Today, development and spread of antimicrobial resistance has become a global public health problem that is impacted by both human and non-human antimicrobial usage (OIE/FAO/WHO 2004a). It is generally acknowledged that any use of antimicrobial agents can lead to the emergence of antimicrobial resistant microorganisms and further promote the dissemination of resistant bacteria and resistance genes (OIE/FAO/WHO 2004a). Furthermore, resistance genes neither respect phylogenetic, geographical nor ecological borders. Thus, the use of antimicrobials in one area, such as aquaculture, can have an impact on the resistance situation in another area, such as in human medicine, and resistance problems in one country can spread to another country.

Antimicrobial resistance deriving from usage of antimicrobials in aquaculture presents a risk to public health owing to either:

- Development of acquired resistance in bacteria in aquatic environments that can infect humans. This can be regarded as a direct spread of resistance from aquatic environments to humans.
- Development of acquired resistance in bacteria in aquatic environments whereby such resistant bacteria can act as a reservoir of resistance genes from which the genes can be further disseminated and ultimately end up in human pathogens. This can be viewed as an indirect spread of resistance from aquatic environments to humans caused by horizontal gene transfer.

1.1.1. Resistant human bacteria

The use of antimicrobial agents in aquaculture can result in an increase in the prevalence of resistant bacteria that can be transmitted to and cause infections in humans. Such direct spread of resistance from aquatic environments to humans may occur owing to (1) consumption of aquaculture food products or through drinking water, and (2) direct contact with water or aquatic organisms, or through the handling of aquaculture food products. These bacteria include:

(1) Motile *Aeromonas* spp, *Edwardsiella tarda*, *Escherichia coli*, *Plesiomonas shigelloides*, *Salmonella* spp., *Shigella* spp., *Vibrio cholerae*, *V. parahaemolyticus*, and *V. vulnificus* (alphabetised list), (WHO, 1999)

(2) Motile *Aeromonas*, *Erysipelothrix rhusiopathiae* *Mycobacterium marinum*, *Streptococcus iniae*, and *Vibrio vulnificus* (alphabetized list).

In most countries human infections caused by *Vibrio* spp. and *Aeromonas* spp. are uncommon compared to *E.coli* and *Salmonella* spp. However, motile *Aeromonas* and *Vibrio vulnificus*, and to a lesser extent non-O1 *Vibrio cholerae* and *Plesiomonas shigelloides*, can cause bloodstream infections, especially in individuals with risk factors such as chronic liver disease and iron overload, as well as in people with immune disorders. Fluoroquinolones are important as first or second line treatment for these potentially fatal infections.

Vibrio vulnificus, *Vibrio parahaemolyticus* and some non-O1 *V.cholerae* serogroups are well-recognized causes of gastrointestinal illnesses, despite the incidence being low in some countries. Motile *Aeromonas* are common causes of self-limiting diarrhoeal illnesses although there is notable geographical variation in incidence, possibly reflecting differences in strains involved. Antimicrobials in general are not required or recommended in the case of self-limiting gastrointestinal illnesses.

Bacteria listed under (2) above are infrequent causes of soft tissue infections that require antimicrobial treatment. In some cases, disseminated infections may also occur.

1.1.2. Resistance genes (horizontal gene transfer)

Development and spread of antimicrobial resistance as a consequence of exposure to antimicrobial agents is widely documented in both human and veterinary medicine. It is also well documented that fish pathogens and aquatic bacteria can develop resistance as a consequence of antimicrobial exposure (Sørum 2006). Examples include *Aeromonas salmonicida*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Citrobacter freundii*, *Lactococcus garviae*, *Yersinia ruckeri*, *Photobacterium damsela subsp. piscicida*, *Vibrio anguillarum*, *Vibrio salmonicida*, *Photobacterium psychrophilum* and *Pseudomonas fluorescens*. For example *Aeromonas salmonicida*, which causes disease in fish of temperate and colder areas, easily develops resistance.

Acquired sulfonamide resistance in *Aeromonas salmonicida* was reported already in 1955 in the USA and, in the 1960s, multiresistant strains were observed in Japan. Later on, multiresistant *Aeromonas salmonicida* have been described from many countries in various parts of the world, and transferable resistance plasmids are commonly detected in these strains (Sørum 2006). Typical transferable resistance determinants are those conferring resistance to sulphonamide, tetracycline, trimethoprim, and streptomycin. The use of quinolones in the

control of bacterial infections from the 1980s resulted in the development of quinolone resistance in strains of *Aeromonas salmonicida*. This resistance in *Aeromonas* was mainly mediated by mutation in the gyrase A gene, *gyrA*, and has so far not been shown to be transferable (Sørum 2006). Development of resistance by shrimp pathogens such as *Vibrio harveyi* due to exposure to antimicrobials has been reported (Karunasagar et al., 1994).

Some bacteria in aquatic environments are phylogenetically related to human pathogens. This increases the probability of spread of resistance genes from aquatic bacteria to human pathogens. Several studies have demonstrated that plasmids harbouring resistance determinants often are transferable from fish pathogens and aquatic bacteria not only to other bacteria within the same genus, but also to *E. coli*. For example, multiresistance plasmids have been shown to be transferable to *E. coli* from *Aeromonas salmonicida*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Citrobacter freundii*, *Photobacterium damsela* subsp. *piscicida*, *Vibrio anguillarum*, and *Vibrio salmonicida* (Sørum 2006). A large multiresistance plasmid conferring resistance to six antimicrobials was shown to be transferable from *Vibrio cholerae* O1 to *A. salmonicida*, *A. hydrophila*, *V. parahaemolyticus*, *V. cholerae*, *V. anguillarum*, *Shigella* spp., *Salmonella* spp. and *E. coli* (Kruse 1995). Plasmids with varying resistance genes have been transferred in vitro from fish pathogens to human pathogens, including *Vibrio cholerae* and *Vibrio parahaemolyticus* (Sorum, 2006). A 21kb plasmid coding for resistance to cephalothin that could be transferred to *E. coli* was isolated from *Vibrio* strains from shrimp ponds (Molina-Aja et al., 2002). Furushita et al. (2003) noted that genes coding for tetracycline resistance in fish farm bacteria and clinical isolates in Japan showed high similarity suggesting that they may be derived from the same source. Further, in laboratory experiments, transfer of tetracycline resistance from marine strains of *Photobacterium*, *Vibrio*, *Alteromonas* and *Pseudomonas* could be transferred to *E. coli* by conjugation suggesting that transfer of resistance from marine bacteria to bacteria associated with the human gut is possible.

It has been shown that mobile genetic elements harbouring resistance determinants can be transferred horizontally equally well between bacteria from terrestrial animals, fish and humans. Transfer experiments in simulated natural microenvironments have shown that the IncU plasmid pRAS1 of *Aeromonas salmonicida*, carrying transferable resistance to sulfonamides, trimethoprim and tetracycline, could transfer directly from the fish pathogen to human *E. coli* on a wooden cutting board in room temperature where salmon was prepared. The transfer frequency (10^{-3}) on the cutting board was similar to the corresponding transfer frequency as on nutrition media in laboratory (Kruse and Sørum, 1994).

The transferability of resistance plasmids from fish pathogens and aquatic bacteria illustrates that these bacteria can act as reservoirs of antimicrobial resistance genes that can be further disseminated, and ultimately reach human pathogens, and thereby add to the burden of antimicrobial resistance in human medicine. In fact, resistance plasmids of fish pathogens and aquatic bacteria have been observed in bacteria of terrestrial, animal and human bacterial flora and environments. Furthermore, the same resistance gene cassettes have been described in both fish bacteria and human clinical isolates. Approximately half of the resistance genes identified in fish pathogens are common to those of human pathogens (Aoki, 2006, unpublished). Thus, bacteria of different environments, including aquatic and hospital environments, can share the same resistance genes (Rhodes et al., 2000; Furushita, et al., 2003, Sorum, 2006). Further, many studies have demonstrated that the genes are located on genetic structures that allow their transfer to other bacteria.

Kim et al (2004) suggested that bacteria from aquaculture sites could be a reservoir of the genes *tet(M)* and *tet(S)* encoding ribosomal protection proteins responsible for resistance to

tetracyclines in several clinical isolates. *Vibrio* spp, *Lactococcus garvieae*, *Photobacterium damsela* subsp. *piscicida* harboured tet(D) gene, while *Vibrio* spp. and *Lactococcus garvieae* harboured tet(S) gene. Molecular characterization shows that some of the antimicrobial resistance determinants in multiresistant *Salmonella* Typhimurium DT104, such as tet(G) causing tetracycline resistance and flo-like gene that confers resistance to both chloramphenicol and florfenicol, are also present in some fish pathogenic bacteria (Bolton et al., 1999 and Brigs and Fratamico, 1999). These molecular characterizations strengthen the evidence that antimicrobial resistance genes can be exchanged between fish pathogens and human bacteria.

Research indicates that 70-80% of the drug used in aquaculture ends up in the environment (Hernandez, 2005). Such environmental contamination with antimicrobials could select for resistance in environmental microflora, and resistance genes could further disseminate and eventually reach human pathogens.

Furthermore, fish pathogens and aquatic bacteria can develop antimicrobial resistance as a response to antimicrobial exposure and such resistant bacteria can act as a reservoir of resistance genes from which the genes can be further disseminated and ultimately end up in human pathogens.

1.2. Antimicrobial residues

Antimicrobial usage in aquaculture for the treatment of bacterial diseases can result in residues of antimicrobials in the food product. The risk to human health of such residues is evaluated as part of the authorization procedure for veterinary drugs. In the international setting, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has developed risk assessment principles for the evaluation of residues of veterinary drugs. JECFA proposes Maximum Residue Limits (MRLs) which are compatible with human health, and which are discussed in the Codex Committee on Residues of Veterinary Drugs and eventually adopted as Codex MRLs by the *Codex Alimentarius Commission*. Recently, an International Workshop on Updating the Principles and Methods of Risk Assessment: Maximum Residue Levels (MRLs) for Pesticides and Veterinary Drugs was organized within the framework of the *Project to Update the Principles and Methods for the Risk Assessment of Chemicals in Food* launched by FAO and WHO in 2002. The report from this workshop describe the data requirements and the assessment process (ftp://ftp.fao.org/ag/agn/jecfa/bilthoven_2005.pdf).

In addition, since the beginning of the assessment of antimicrobial drug residues, JECFA has developed specific guidance and a decision tree for the determination of microbiological ADIs. This guidance has recently been harmonized with the guidance adopted by VICH (Veterinary International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products <http://www.fda.gov/cvm/vich.html#Updates>), VICH GL36. Thus, the risk assessment framework for residues of antimicrobial veterinary drugs has been developed and is used on the international, as well as on the national and regional, level. The decision tree for the establishment of a microbiological ADI includes the potential for the drug in question to develop antimicrobial resistance in the human gut microflora, including the mechanism for resistance development.

In the case where a veterinary drug has not been approved for use in aquaculture or does not have Codex MRLs, the risk to public health is not known and may, if present at sufficient concentration, represent a hazard for consumers of aquaculture products of fish or shellfish which have been treated with antimicrobial drugs.

2. Hazard characterization

2.1. Antimicrobial resistance

The consequences of antimicrobial resistance in bacteria causing human infections include:

(1) Increased frequency of treatment failures and increased severity of infection as a result of antimicrobial resistance may be manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, or higher mortality (OIE/FAO/WHO 2004a). Although there are no examples involving cases from aquaculture products, prolonged duration of illness has been demonstrated in case-control studies of fluoroquinolone-resistant *Campylobacter* (Smith et al, 1998; Neimann et al, 2003). Prolonged duration of illness has also been demonstrated among persons infected with nalidixic acid resistant *Salmonella Typhi* treated with fluoroquinolones. The association between an increased frequency of antimicrobial resistance *Salmonella* and an increased frequency of hospitalization has been demonstrated in several studies. The same phenomenon as demonstrated for *Salmonella* and *Campylobacter* can occur with other resistant human pathogens, in which resistance might have originated in aquaculture.

(2) Antimicrobial agent use in humans disturbs the microbiota of the intestinal tract, placing such individuals at increased risk of certain infections. Individuals taking an antimicrobial agent, for any reason, are therefore at increased risk of becoming infected with pathogens resistant to the antimicrobial agent.

2.2 Antimicrobial residues

If present in concentrations above the established maximum residue limits, or if the drug is used without appropriate authorization based on scientific assessment of the benefit and risk of the treatment, residues can present a hazard in products from aquaculture.

2.2.1 Toxicological aspects

Chloramphenicol was evaluated by JECFA on several occasions as well as other agencies (IARC and CVMP). Concerns have been expressed about the genotoxicity of chloramphenicol and its metabolites, its embryo- and fetotoxicity, its carcinogenic potential in humans and the lack of dose response relationship for aplastic anemia in humans. It has been concluded that chloramphenicol is not suitable for use in food producing animal species as no ADI or MRLs could be established. However, there are no reported cases of aplastic anaemia attributed to consumption of chloramphenicol residues in foods.

JECFA also concluded that there was no evidence that chloramphenicol could be synthesized naturally in detectable amounts in soil.

Chloramphenicol presents a particular threat to human health as it can cause an idiosyncratic dose-independent aplastic anemia in humans, which can be induced by low concentrations of chloramphenicol. (Sundlof, 1993). Aplastic anemia is irreversible and has a 70% case fatality rate. Those who recover experience a high incidence of acute leukaemia. The probability is about 1 in 25 000 if exposed to oral treatment with chloramphenicol.

Drug allergies are generally considered to be type 1 immune response mediated through IgE. Symptoms include urticaria, angioedema and might include anaphylaxis. Penicillin is the

most commonly implicated antimicrobial in adverse reactions from foodborne residues, causing penicillin hypersensitivity or skin disease unrelated to penicillin allergy. Penicillin residues as low as 5-10 IU are capable of producing allergic reactions in previously sensitized persons (Sundlof 1993). The extent of use of penicillin in aquaculture is most probably low due to the fact that penicillin rapidly degrades in aqueous solutions.

Many antimicrobials other than penicillin – including other beta-lactams, streptomycin (and other aminoglycosides), sulfonamides and, to a lesser extent, tetracyclines - are known to cause allergic reactions in sensitive persons. But, apart from a single report of a reaction to meat suspected of containing streptomycin residues, we are not aware of any reports of foodborne allergic reactions resulting from residues of any antimicrobial other than penicillin (Sundlof 1993).

Increasing concern about the carcinogenic and mutagenic potential and their thyroid toxicity has led to decreased use of sulfonamides. Research has shown that chronic dietary exposure to sulfamethazine produces a statistically significant increase in thyroid follicular cell adenomas in both rats and mice, and a statistically significant increase in thyroid follicular cell adenocarcinomas in rats (Sundlof 1993).

2.2.2. Effects on human intestinal flora

The principal concern is to which degree antimicrobial residues in food may affect human health either by: (i) exerting a selective pressure on the dominant intestinal flora; (ii) favouring the growth of micro-organisms with natural or acquired resistance; (iii) promoting, directly or indirectly, the development of acquired resistance in pathogenic enteric bacteria; (iv) impairing colonization resistance; or (v) altering metabolic enzyme activity of the intestinal microflora (Hernandez, 2005). Although limited knowledge is available in this area, a few studies indicate that at low level of exposure effects on the human intestinal microflora might occur (EMEA 2001).

However, the risk assessment performed to establish a microbiological ADI takes into account the potential for development of resistance, using models with human faecal material or in vivo studies.

3. Exposure assessment

3.1. Prevalence of antimicrobial resistant human pathogens

The risk of human infections from the organisms listed in 1.1.2 has been assessed by FAO and WHO and determined to be low or very low (WHO 1999). However, although there are large variations depending on regions and environmental conditions, antimicrobial resistance in many of these bacteria from aquatic environments is widespread. It is uncertain to what degree the resistance is a result of antimicrobial usage in aquaculture. It is likely that usage in other areas such as human medicine and terrestrial animals play a role.

Salmonella spp. and *E. coli* strains, including resistant strains, can be found in aquatic environments as a result of contamination with such bacteria from human, animal or agricultural environments. The resistance is caused by usage of antimicrobials in humans or terrestrial food animals. Sewage contamination or run-off from agricultural areas with grazing animals to aquaculture operations can result in the presence of resistant *Salmonella* spp. and *E. coli* in products of aquaculture. The similar picture applies to *Shigella* spp., but for this

pathogen, which is a strictly human pathogen, antimicrobial usage in humans is the promoter of resistance development and spread. In some aquaculture environments, human pathogens deriving from terrestrial animal or human wastes may be incapable of extensive cell division, limiting the extent to which usage of antimicrobial agents in aquaculture can exert a selective pressure for the emergence of resistant variants. However, in some climatic and aquaculture systems, there might be cell division and usage of antimicrobial agents in aquaculture can exert a selective pressure for the emergence of resistant variants.

Vibrio spp. are marine bacteria of which some can be pathogenic to humans. Resistance in *Vibrio cholerae* and *Vibrio parahaemolyticus* can be a result of human usage of antimicrobials, but may also be a consequence of use of antimicrobials in aquaculture.

The risk that resistant bacteria from aquaculture may be present in treated drinking water supply is remote. In areas where drinking water is not treated, resistant bacteria from aquaculture may reach drinking water supply (Hernandez, 2005).

3.2 Prevalence of antimicrobial resistance genes

It is well documented that antimicrobial resistance develops and spreads in fish pathogens as a consequence of exposure to antimicrobials. Available literature shows that resistance is widespread in fish pathogens and, in general, that resistance is more prevalent where the usage is high.

The resistance genes in fish pathogens are often the same as those found in human pathogens, and most of these genes are transferable. Thus, fish pathogens act as a reservoir of resistance genes that can be transmitted horizontally to human pathogens through different pathways. Transfer of R Plasmid and emergence of new drug resistance gene cassettes have been reported in human and fish pathogenic bacteria in aquatic environments.

Because antimicrobials used in aquaculture can be deposited in the environment, there is potential for a selective pressure on environmental bacteria. As a result, there is also potential for the establishment of a reservoir of resistance genes for further dissemination, which could ultimately reach humans.

3.3 Antimicrobial residues

The public health risk associated with antimicrobial residues depends on the quantity of the antimicrobial encountered or consumed, i.e. the exposure. In general, the lower the exposure, the lower the risk. Public perception that foodborne residues pose a major health risk is not supported by actual case reports. The FAO/OIE/WHO consultation on scientific issues related to non-human usage of antimicrobials held in Geneva, in December 2003, concluded that residues of antimicrobials in foods, under present regulatory regimes, represent a significantly less important human health risk than the risk related to antimicrobial resistant bacteria in food.

The use of water and food as the most common administration route in aquaculture helps to obtain a uniform dose and avoid any potential for high localized concentration that might accumulate at the site of injection during intramuscular or subcutaneous routes of administration, such as in terrestrial animals. Strict adherence to withdrawal times is nevertheless critical.

Several factors contribute to the drug residue problem. In many countries there is a lack of labeling advising on how to use the drugs appropriately. In countries with labeling, violations result from the use of the drug in some manner that is inconsistent with the labeling. Failure to adhere to withdrawal times is the most usual reason, while use of an unapproved drug, and administration of increased dosages, also results in violative residues. In most countries where antimicrobials are licensed for use in aquaculture, withdrawal times that ensure safety to the consumers are set. Non-compliance with these withdrawal times presents a risk to public health.

Most countries have implemented monitoring or surveillance programmes in regard to drug residues in food animals, including farmed fish.

In most countries, chloramphenicol has been banned for use in food producing animals, including aquaculture, because of the risk of severe human disease associated with chloramphenicol residues. An acceptable daily intake (ADI) has never been allocated for chloramphenicol and, consequently, a maximum residue limit (MRL) has not been assigned. This has resulted in the restriction of its use in veterinary medicine to non-food use. Despite these restrictions, chloramphenicol has been detected in national monitoring programmes during the past years and these residues have caused safety concerns. Shrimps, prawns and food products from aquatic animals were among the commodities in which the drug was detected (Sixty-second Report of the Joint FAO/WHO Expert Committee on Food Additives, WHO Technical Report Series, No. 925, 2004; Ababouch et al., 2005). Although there are no reported cases of aplastic anaemia attributed to consumption of chloramphenicol residues in food, the probability of such an event cannot be excluded.

3.4. Consumption data

With the increasing human consumption of products of aquaculture, the probability of exposure to potentially occurring antimicrobial resistant bacteria, resistance genes or antimicrobial residues in seafood is increasing. This probability increases if seafood is consumed with little or no heat treatment.

3.5. Contact with products of aquaculture

With the increasing importance of the aquaculture industry and increasing consumption of products of aquaculture, human exposure to resistant bacteria and resistance genes in aquaculture and products of aquaculture through professional activities or food handling also increases. This type of exposure also represents a potential route for spread of resistant bacteria and resistance genes from aquaculture products to humans.

4. Risk characterization

The risks identified in relation to antimicrobial use in aquaculture are the direct transfer of resistant bacteria, the development of a reservoir of transferable resistance genes in bacteria in aquatic environments, and antimicrobial residues. In aquaculture, the issue of direct transmission of resistant human pathogenic bacteria represents a low risk as such bacteria are rarely transmitted through aquaculture products. Comparatively, the greatest risk associated with antimicrobial use in terrestrial animals is the direct transmission of resistant zoonotic bacteria through the food chain, as compared to the issue of the development of a reservoir of transferable resistance genes. The greatest risk to public health associated with antimicrobial use in aquaculture is assumed to be the development of a reservoir of transferable resistance

genes in bacteria in aquatic environments. Such genes can be disseminated by horizontal gene transfer to other bacteria and ultimately reach human pathogens, and thereby potentially cause treatment problems due to resistance. Antimicrobial residues represent a low, but still significant public health risk.

5. Data gaps and future research needs

- There is a need for more national and regional data on prevalence of antimicrobial resistance in various bacteria and different production types.
- There is a need for more data on the conditions in the aquaculture environment including sediments for selection of resistance to antimicrobials.
- There is a need for better national and regional data on usage of different antimicrobials in different production types.
- There is a need for more national and regional data on the occurrence of residues of various antimicrobials in aquaculture products from different production types.
- There is a need for more knowledge on spread of resistance genes from aquatic bacteria and fish bacteria to human pathogens.
- There is a need for more knowledge on consumption of aquaculture products and consumption habits in various regions.
- There is a need for better in vitro and in vivo methods for determining the effects of low concentrations (residues) of antimicrobials on the human intestinal microflora.
- There is a need for more research in regard to pharmacological and pharmacokinetic aspects of antimicrobials used in aquaculture in order to provide a more exact approach to develop MRL values.

6. Capacity building

There is a need to support and assist developing countries in their efforts regarding:

- implementation of preventive measures (hygiene, environmental conditions, and vaccines);
- implementation of prudent use guidelines;
- regulatory control of antimicrobial usage; and
- monitoring of antimicrobial use and antimicrobial resistance.

7. Recommendations

- Measures should be developed and implemented at national and international levels to prevent the development and spread of antimicrobial resistance in aquaculture.
- Countries should be encouraged to implement regulatory systems to prevent the occurrence of antimicrobial residues in aquaculture products, both for the national and international markets.
- Studies to assess the likelihood of gene transfer (intra- and inter-species) in aquaculture and the natural environment should be encouraged. These studies should include investigations of the stability of inheritance of the transferred determinants.
- Capacity to monitor the usage of antimicrobial agents in aquaculture should be built up.

- Member countries should undertake development, harmonization and implementation of methods for monitoring the prevalence of resistant bacteria, resistance genes and antimicrobial residues in products from aquaculture and in the aquatic environment.
- Given the lack of data, in respect of many aspects of antimicrobial use in aquaculture, a preliminary study designed to prioritize the various risks that have been identified should be performed. Risks with a high priority should then be investigated in a full qualitative risk assessment.

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PART 2 - STRATEGIES AND RECOMMENDATIONS TO REDUCE THE RISK OF ANTIMICROBIAL RESISTANCE ARISING FROM THE USE OF ANTIMICROBIALS IN AQUACULTURE

1. Introduction

The risks to people from the use of antimicrobials in aquaculture can be reduced by the adoption of a number of strategies that are discussed and detailed in this section. These include taking actions to decrease the frequency of infections occurring in farmed aquatic animals through the use of optimal animal husbandry and attention to issues that improve the conditions under which they are grown. Preventive measures such as the use of vaccines and improved biosecurity have also been successful. Disease prevention will decrease the amount of antibiotics that need to be used and will also decrease the “pressure” that induces and amplifies antibiotic resistant bacteria. These resistant bacteria can cause problems with the therapy of bacterial infections of fish and also problems for people if resistant bacteria transfer to people via the food chain or via the environment.

If antibiotic therapy is needed then resistance problems can be minimized when appropriate antibiotics are used prudently for specific diseases and indications. Some antibiotics are classified as “critical” to human health and their use will need special consideration. If resistance develops to these critical antibiotics, and if these resistant bacteria or other bacteria carrying these resistant genes spread to people and animals, this will limit treatment that may have clinical consequences.

2. Risk management options

2.1 Reducing over-use and mis-use of antimicrobials²³

The WHO Global Principles for Containment of Antimicrobial Resistance in Animals Intended for Food (Annex 4), the OIE International standards on antimicrobial resistance in (Annex 5), the Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (Annex 6) and the codex Code for fish and Fishery Products (Section 6 - Aquaculture Production) (Annex 7) provide recommendations on the responsible and prudent use of antimicrobial agents in veterinary medicine, to reduce the overuse and misuse of

² In accordance with the WHO consultation entitled "Critically important antibacterial agents for human medicine" (WHO, 2005), the WHO Principles should be updated by replacing the terms "highly important (antimicrobial agents) in human medicine" and "essential (antimicrobial agents) for human medicine" with "critically important antimicrobial agents for human medicine".

³ OIE - Terrestrial Animal Health Code / Appendix 3.9.3: Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine. In article 3.9.3.3 the OIE Animal Health Code states that "the evaluation of antimicrobial agents for food producing animals should focus on each individual antimicrobial product and the findings not be generalized to the class of antimicrobials to which the particular active principle belongs". This OIE rationale differs from the rationale of the WHO "Critically Important Antimicrobial Agents for Human Medicine for Risk Management Strategies of Non-human Use" report of the working group consultation in Canberra, Australia (2005) which evaluated for risk management strategies that classes of antimicrobials used for non-human use had to be considered instead of separate evaluation of each antimicrobial agent. There are different rationales which may affect the future availability of certain antimicrobials even though they have been used in aquaculture for many years. Some of the antimicrobials used in aquaculture are grouped in the WHO document along with later generation antimicrobials that are important for human health that should be preserved for human use. Evaluation of individual antimicrobial agents may be required, based upon scientific data and in order to enable the ongoing usage and preserve certain antimicrobials for aquaculture without compromising human health.

antimicrobials in animals for the protection of human health. The WHO Principles, OIE Guidelines and Codex Code of Practice include recommendations for regulating the use of antimicrobials (authorization, manufacture, and distribution) and promoting prudent use of antimicrobials that are relevant to both food and non-food animals. Although aquaculture was not specifically considered when the WHO Principles, the OIE Guidelines and the Codex Code of Practice on antimicrobial resistance were adopted, the Codex Code of Practice for Fish and Fishery Products does not cover extensive fish farming systems or integrated livestock and fish culture systems that dominate aquaculture production in the world. These principles, guidelines and codes also pertain to the use of antimicrobial agents in aquaculture, including ornamental and other non-food aquatic animals, with the following additional considerations:

(1) Critically important antimicrobials for human health. Owing to the limited availability of registered veterinary medicines in aquaculture, extra-label use is common in many countries, and may be an important component of control.

(i) In accordance with WHO principles, relevant authorities which regulate extra-label use of antimicrobials in animals, including aquaculture animals, should consider restriction of critically important antimicrobials for human medicine. (Principle 4, WHO).

(ii) In accordance with WHO principles, those antimicrobials judged to be critically important for human medicine should be restricted and their use in animals, including aquatic animals, should be justified by culture and susceptibility results. (Principle 6, WHO).

(2) Horizontal gene transfer is an important concern related to the use of antimicrobial agents in animals including aquaculture. However, since the transfer of resistant zoonotic pathogens directly through the food supply is uncommon with aquaculture, horizontal gene transfer is of increased importance, compared to direct zoonotic transfer through the food supply, in aquaculture.

(i) In accordance with WHO principles, decisions concerning the registration of veterinary antimicrobial substances should consider the impact on human health of antimicrobial resistance developing in aquatic animals and the surrounding aquatic environment. (Principle 7, WHO).

(ii) In accordance with WHO principles, the strategic aim of policies expressed in guidelines on prudent use should provide advice on optimal therapeutic effect and/or protection of animals at risk and on the control of antimicrobial resistance in animals, zoonotic bacteria, and the surrounding aquatic environment. (Principle 24, WHO).

(3) Since an important proportion of aquatic animals raised for the global aquaculture industry are raised in countries with few regulations and limited enforcement for the authorization of antimicrobial agents used in animals, efforts are needed to promote development and enforcement of such a regulatory structure. Efforts are also needed in countries with an established regulatory structure to encourage availability of appropriately evaluated antimicrobial agents for aquaculture.

(4) Since in many countries an important proportion of antimicrobial agents used in aquaculture is administered under the direction of veterinarians and veterinary para-professionals (e.g. animal health professionals), efforts are needed to educate these individuals about prudent use of antimicrobial agents.

(5) Since in many countries an important proportion of antimicrobial agents used in aquaculture are administered with limited or no professional supervision or guidance, the development of extension services is needed.

2.2 Disease prevention and infection control

To minimize the use of antimicrobials and avoid the negative impact of antimicrobial resistance, it is essential to prevent and/or control bacterial diseases of aquatic organisms.

(1) Infection control and prevention requires accurate diagnosis of disease conditions to ensure the proper application of antimicrobial therapy (OIE Manual of Diagnostic tests for Aquatic Animals). Another aspect in the prevention and control of infectious disease in aquaculture is the need for improvement of diagnostic practices including the development and implementation of rapid diagnostic methods. Many areas lack adequate veterinary and diagnostic support.

(2) Implementing periodical disease surveillance and management health plans is important to maintain the health status of the aquatic organisms including ornamental fish. Knowledge concerning the nature of pathogens, source of infection, carriers, mode of transmission, epidemiology, etc, of disease is needed for disease management.

(3) Monitoring of the health status of ornamental fish is encouraged as it may act as a source of infection and antimicrobial resistance for aquatic animals and humans. In order to maximize the ability to withstand disease, it is important to maintain optimal environmental conditions such as stocking densities, good water quality, proper feeding and high standards of hygiene for aquatic animals.

(4) Effective environmental management such as optimal site selection, water source, facility design, fish handling, transport system and the efficient waste removal are important for successful fish culture and disease prevention (CAC/RCP 61-2005).

(5) Proper feeding (quantity and quality) is important, not only for growth and prevention of nutritional diseases, but also for overall health. Using animal by-products may constitute fish health problems and public health hazard through transmission of zoonotic diseases and antimicrobial resistance genes.

(6) Sanitation and disinfection of aquaculture and hatchery facilities are very important to control both vertical and horizontal transmission of diseases.

(7) Vaccination is an important measure in relation to disease prevention in finfish. Vaccines are available for many of the major infectious diseases problematic in aquaculture, and by the application of such vaccines the need for antimicrobials can be reduced substantially.

(8) Other methods for improving the immunity of aquatic animals against diseases may be helpful. These include:

(i) Selective breeding is an important approach to obtaining more tolerant strains of aquatic animals against infectious pathogens.

(ii) Immunostimulants, including bioactive natural products, may represent a new approach for the control of disease in aquaculture, but need further evaluation.

(9) Biosecurity practices used for disease control are necessary. Adoption of quarantine measures together with establishment and enforcement of national and international regulations will help prevent the transfer of infectious agents (CAC/RCP 52-2003).

(10) Regulatory measures together with an appropriate legal framework with the necessary powers for policy decision making and for the practical application of regulations that are accepted by aquaculture industry are essential for disease prevention and control in aquatic animals.

2.3 Environmental management

2.3.1 Manure

Human and animal waste can be added to aquaculture ponds as a fertilizer to increase plant and phytoplankton growth, which fish then eat. This manure may carry antimicrobial agents. Since manure contains enteric bacteria, some of which may be antibiotic resistant, particularly if the animals or people have received antibiotics, the use of manure should be avoided whenever possible. If manure is used, it should be processed to reduce enteric bacteria.

2.3.2 Waste

There will be an antimicrobial fraction that is lost to the water column following leaching of the medicated feed, and a portion of non-absorbed medication excreted by the aquatic organism in the urine and faeces. Recuperation of the faecal portion by using waste recuperation techniques such as sedimentation or filtration will help reduce the quantity of antimicrobial released to receptor watersheds. The binding of certain antimicrobials with benthic sediments, as well as degradation by microbial processes and exposure to sunlight, will decrease the quantity of available active medication in the environment.

Care will be needed with any sludge or waste water released for ponds if used for people or animals as it may contain resistant bacteria and/or traces of antimicrobials. Care will also be needed with waste water and sludge applied to foods (e.g. vegetables).

2.3.3 Location of fish farms

The rates of water exchange need to be taken into account and dilution factors for any antibiotics that will leech from feeds and may be present in effluents as these will otherwise be deposited into and accumulate in the layers below the “fish farm”. Thus the relevant national authorities should take into consideration the environmental impact in decisions on where to locate and/or how often to move [aquatic ponds, net pens, containers and sea farms].

2.4 Risk analysis framework

The use of antimicrobials in aquaculture should be seen within a general framework for risk analysis of antimicrobial resistance in relation to the use of antimicrobials in animals. A future Codex *Ad-Hoc* Task Force on Antimicrobial Resistance with respect to Food Safety should work with input from OIE to develop such principles as well as guidelines for risk assessment. Guidelines for risk assessment could be harmonized between the existing OIE guidelines, *Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals*, (http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.4.htm) and general guidelines from Codex. Risk assessment to support the risk analysis process

could be envisaged within the framework of the Joint FAO/WHO Expert Meeting on Microbiological Risk Assessment (JEMRA) with the additional expertise of OIE. The development of capacity to assess the relative importance of human antimicrobial use as compared to animal use is an important area for future work. There is a need for increased scientific and surveillance efforts to provide data to fit the risk assessment frameworks developed. Data input for these efforts could be sought from national authorities as well as scientific institutions and industry.

3. Risk management: implementation

(1) The establishment of regulations which concern the use of antimicrobials should be promulgated. These should establish permitted antimicrobial products as well as allowable withdrawal times.

(2) The development of extension services, in collaboration with producers and producer associations where they exist, are necessary to provide information to producers concerning applicable regulations and appropriate antimicrobial usage. The importance of this professional expertise is also relevant concerning the application of judicious use principles. Expertise with the different aquatic species, as well as pathology, pharmacology, immunology, physiology and other connected disciplines is a vital resource when planning disease control strategies.

(3) Control measures for the importation of antimicrobials and dispensing their use in aquaculture should be established.

(4) The imposition and enforcement of regulations concerning antimicrobial residues in aquaculture products for domestic and export markets may help to reduce the use of forbidden substances.

(5) The intervention of trained professionals (veterinarians and veterinary paraprofessionals) on the aquaculture site is vital for the dissemination of information concerning appropriate antimicrobial usage as well its enforcement.

(6) The imposition of food safety standards by importing countries and/or enterprises are likely to have a positive reinforcement effect upon avoidance of antimicrobial residues.

4. Risk management: capacity building

(1) The development of adequate diagnostic support is essential for aquaculture industries in order to ensure the appropriate utilization of antimicrobials.

(2) The development of an adequate enforcement infrastructure is necessary to assure adherence to existing regulations concerning antimicrobial use in aquaculture.

(3) The development of surveillance infrastructure will be necessary to evaluate the development of antimicrobial resistance as well as to obtain information concerning antimicrobial use. This data is necessary for risk analysis.

(4) The approval process for antimicrobials and vaccines specifically designed for aquatic animal species should be optimized for rapid movement through the regulatory process,

ensuring efficacy and availability of the product, while limiting impact on the human population.

(5) The development of technical expertise is important for the implementation of regulations. Owing to the paucity of veterinarians and/or paraveterinary professionals available in certain regions, universities and other learning institutions should be encouraged to include training relevant to aquatic species in their *curriculae*.

(6) The development of research capacity which addresses antimicrobial residue development and connected issues should be supported. Additional research efforts should be undertaken which address methods of disease control that decrease the need for antimicrobials.

5. Identified gaps

The mechanisms and probability of antimicrobial resistance factor transfer in aquatic environments is poorly understood. The absence of most human foodborne pathogens associated with aquatic animal husbandry suggest that, if the use of antimicrobials in aquatic environments is a hazard, horizontal resistance factor transfer would be the predominant mechanism. The prevalence of such factor transfer is unknown as are the factors that encourage horizontal transfer. Knowledge, programmatic, and management gaps can be identified and, if filled, would foster prudent antimicrobial use, perhaps reduce general use of antimicrobials and provide a means to measure progress.

(1) The efficacy of antimicrobial therapeutic agents under various clinical conditions is ill-defined. Post-marketing antimicrobial surveillance programmes need to be developed to guide stakeholders and authorities in refining appropriate use.

(2) Horizontal resistance factor transfer dynamics in aquatic environments is complex and poorly understood. Research needs to be completed to determine exposure pathways and identify opportunities to interdict R factor transfer.

(3) The perceived need to use antimicrobial therapeutic agents can be reduced if alternatives to antimicrobials are made available. International efforts to foster vaccine development and approval of other immunomodulators should be encouraged. There is a need to develop fast track vaccine licensing procedures.

(4) There are significant differences among nations regarding the rigour of the drug approval process and the enforcement of existing regulations for use. There is a need for international harmonization of the drug approval process, and of the methodology to determine antimicrobial resistance, and establishment of clinically relevant breakpoints. There is a need for consistent national enforcement of antimicrobial use regulations.

(5) To help guide industry and authorities there is a need for regional data:

(i) on the prevalence of antimicrobial resistance in various bacteria and different aquaculture production types;

(ii) on the usage of different antimicrobials in different production types; and

(iii) on the occurrence of residues of various antimicrobials in different production types;

(iv) on the consumption of seafood in various regions and different subpopulations, to define exposure levels.

(6) There is a need for:

(i) more research in regard to pharmacological and pharmacokinetic aspects of antimicrobials used in aquaculture in order to provide a more precise approach to develop MRL values;

(ii) epidemiological studies in aquatic animal disease characteristics to assist in reducing disease prevalence and perceived or real need to use antimicrobials.

(7) In various regions of the world there is a paucity of qualified veterinary and paraveterinary professionals able to advise fish farmers. Such professionals are important for ensuring compliance with guidelines for the judicious use and application of good aquaculture practices.

(8) There is a need to enhance training curricula at veterinary and fisheries schools and encourage broad participation by students.

(9) There is a need to increase the availability of accurate diagnostic services at regional and farm levels (diagnostic kits). Extension services are lacking in some regions.

(10) There is a lack of risk benefit data.

(11) There is a lack of producer associations.

Suggestion for a gap

Although not specifically considered within the terms of reference of this Expert Consultation, it was the impression of participants that future activities could be beneficial in relation to promoting evaluation at a more general, holistic level of both benefits and risks related to, for example, fish production and consumption. Such work would be especially important in relation to future risk communication efforts in this area. Consideration of broader risk perception issues could also be included within such future work, enabling sensible interaction with decision-makers, as well as consumers and other stakeholders, during the different parts of the evaluation and risk analysis process. Benefits to be considered in relation to this could be: (a) the benefit of a diet including sea-food, (b) the socioeconomic benefits of sensible aquaculture development, and (c) the economic and health benefits of risk avoidance. In general, developments towards risk-benefit evaluations are at an initial stage within international and especially certain national settings relative to the presentation of, for example, fish consumption and chemical contamination of fish. More holistic evaluations have also been suggested for the production of genetically modified food. Should the need for such broader evaluations be acknowledged, a number of issues would need further deliberations, e.g. development of principles and models for benefit assessment, suggestions for responsible, international bodies for such assessment and construction of broader frameworks for integrated risk and benefit analysis.

6. Recommendations *(not listed in order of priority)*

- WHO has defined a list of “critically important drugs for human medicine” that require special risk assessment and management, and this list should be considered in the use of antimicrobials in animal health.
- An OIE list of antimicrobials of veterinary importance for animal use is in the process of further refinement according to the type of usage. OIE should specifically address antimicrobial use in aquaculture.
- Regulations at the national level should be established for the approval of antimicrobials used in aquaculture with a view to international harmonization. These should include approval of antimicrobials for all relevant aquatic species as well as recommending allowable withdrawal times.
- All uses of antimicrobials, including off-label and extra-label use should also be regulated. Governments should ensure these regulations are enforced. Controls of import and dispensing of antimicrobials should also be established. Drug residue surveillance programs for aquaculture products should be implemented.
- Antimicrobial agents used in aquaculture should be used prudently and in accordance with the WHO Global Principles and with the relevant Provisions of the OIE Terrestrial Animal Health Code and Codex texts made applicable to aquatic animals (appendix 4, 5 and 6: guidelines for prudent use of the three organizations).
- A practical, feasible and cost effective approach should be developed and implemented, building on the work of FAO, NACA (Network of Aquaculture Centers in Asia) and others to strengthen aquaculture extension support and technical advice and assistance to small scale aquaculture to increase awareness, implement good aquaculture practices⁴, and strengthen government and industry institutions for aquatic animal health. The strategies should be integrated within an overall approach for poverty alleviation with particular emphasis on access to credit (micro-credit) and to extension support services.
- Provision of basic diagnostic services and tools should be the joint responsibility of governments and the private sector to ensure that they are accessible to producers and the aquaculture sectors at all levels. Governments should promote appropriate aquatic animal health management framework through national centers, farmer associations and extension services is available for aquaculture at local, national and regional level including on farm diagnostic services, rapid diagnostic kits, simple tests such as disk diffusion, as well as high technology diagnostic centres. This framework should include trained professionals as well as specialized diagnostic centres that will monitor pathogen emergence and clinical relevance.
- Programs to monitor usage and antimicrobial resistance in bacteria from farm-raised aquatic animals and their environment should be implemented based on existing guidelines (OIE Guidelines for the harmonization of antimicrobial resistance surveillance and monitoring programmes, which may be found at the following

⁴ FAO is currently working on technical guidelines for the improvement of safety and quality in aquaculture, which should be field-tested in early 2007 and finalized the same year.

website: http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.1.htm and for the monitoring of the quantities of antimicrobials used in animal husbandry, which may be found at: http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.2.htm)

- Veterinarians, veterinary paraprofessionals (e.g. aquatic animal health specialists), fish farmers, medical practitioners and authorities, should be kept regularly informed, at least annually, about surveillance results and trends. National databases should be developed to achieve efficient communication. Antimicrobial susceptibility testing should be performed according to standardized methods using appropriate quality controls and be reported quantitatively to allow comparisons of results. Susceptibility testing methods in aquatic bacterial species should be harmonized.
- Training and technical assistance should be provided to build capacity and infrastructure particularly in developing countries to strengthen government institutions, industry support services and extension services in the areas of prudent antimicrobial use, good aquaculture practices and food safety. Veterinary institutions should be encouraged to promote aquatic animal health in the training of veterinarians.
- Producer associations should be promoted at national or regional levels to improve management strategies for aquatic animal farming, reduce usage of antimicrobials and improve economic viability of small farmers.
- Programme should be developed to increase aquatic animal fitness for aquaculture. Such a programme should include selective breeding for optimal aquatic animal performance, disease resistance and other parameters of importance to farming success.
- Tools should be developed that foster optimal rearing environments for aquatic animal production. Special consideration should be given biocontrol opportunities and improvements in biosecurity.
- Efficacious vaccines and improved systems for mass vaccination of finfish should be developed and implemented in order to reduce antimicrobial utilization. Optimization of vaccine licensing procedures should be promoted.
- Post-marketing antimicrobial surveillance programmes should be developed to monitor changes in clinical efficacy and frequency of treatment failures. Veterinarians, veterinary paraprofessionals and aquatic animal farmers should be kept regularly informed about surveillance results and trends. A standardized database should be developed to achieve efficient communication and allow comparisons.
- There is a need for a coherent framework for risk analysis of antimicrobial resistance in relation to the use of antimicrobials in animals intended for food including aquatic animals. This framework should also enable future linkages to broader evaluations, including comparisons of the relative importance of animal versus human use as well as risk-benefit evaluations.
- The future Codex Ad-Hoc Intergovernmental Task Force on Antimicrobial Resistance with respect to Food Safety should work in close collaboration with OIE to develop risk analysis principles and risk assessment guidelines. Within this process a full risk assessments should be developed in priority areas.

**Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use
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**Joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use
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AGENDA

<i>Tuesday, 13 June 2006</i>		
09.00 – 10.00	<p>SESSION I: OPENING OF MEETING</p> <ul style="list-style-type: none"> • Welcome and opening remarks • Election of chairperson and vice-chairperson • Appointment of rapporteur • Adoption of the agenda <p>Introductory statement on behalf of FAO, OIE, WHO and CODEX</p>	<p>Dr C. J. Moon, Commissioner, KFDA</p> <p>Chairperson</p> <p>Dr Jørgen Schlundt, WHO</p>
10.00 – 10.30	Tea/Coffee break	
10.30 - 12.30	<p>SESSION II: DRAFTING GROUP PAPERS</p> <p>Presentation of draft paper on aquaculture production and utilization</p> <ul style="list-style-type: none"> - World aquaculture production and contribution to food security (production volume and value, producing countries, species, consumption, utilization, trade) - Aquaculture technology and aquaculture systems, use of antimicrobials in aquaculture - Technological developments and future trends <p>DISCUSSION</p>	<p>P. Christofilogiannis</p> <p>C. Lavillapitogo</p> <p>D. Prater</p>
12.30 – 13.30	Lunch	

13.30 – 15.30	<p>Presentation of draft paper on animal health issues</p> <ul style="list-style-type: none"> - Benefit assessment for animal health - Exposure assessment - Hazard identification - Risk assessment (Animal Health risk and human exposure to antimicrobial residues and antimicrobial resistance) - Risk Management (Prudent use) <p>DISCUSSION</p>	<p>B. Guichard</p> <p>P. Smith</p> <p>V. Aldaysanz</p> <p>C. Uhland</p>
15.30 – 16.00	Coffee break	
16.00 – 18.00	<p>Presentation of draft paper on public health issues:</p> <ul style="list-style-type: none"> - Risk assessment : human health consequences of use of antimicrobials in aquaculture (considering resistant bacteria, resistant genes, residues, environmental aspects) - Hazard identification, hazard characterization, exposure assessment - Establishment of a risk profile including consideration of factors that might contribute to an increase in antimicrobial resistance - Identify gaps , needs for future research and capacity building - Risk management options <p>DISCUSSION</p>	<p>F. Angulo</p> <p>H. Kruse</p> <p>P. Collignon</p> <p>I. Karunasagar</p> <p>O. Heuer</p>
Wednesday, 14 June 2006		
0900 – 10.30	<p>SESSION III: WORKING GROUP SESSIONS</p> <p>Plenary:</p> <p>Formation of Working Groups 1 and 2 Election of chairpersons and rapporteurs</p> <p>Working Group 1: Risk assessment approach Working Group 2: Risk management options</p>	
10.30 – 11.00	Coffee break	
11.00 – 13.00	<p>Working Group 1: Risk assessment approach Working Group 2: Risk management options</p>	
13.00 – 14.00	Lunch	

14.00 – 15.30	Working Group 1: Risk assessment Working Group 2: Risk management options	
15.30 – 16.00	Coffee break	
16.00 – 18.00	Plenary: Restitution Working Groups 1 and 2	
Thursday, 15 June 2006		
09.00 – 10.30	Working Group 1: Risk assessment approach Working Group 2: Risk management options	
10.30 – 11.00	Coffee break	
11.00 – 12.30	Plenary: Restitution Working Groups 1 and 2	
12.30 – 14.00	Lunch	
14.00 – 15.30	Working Group 1: Risk assessment Working Group 2: Risk management options	
15.30 – 16.00	Coffee break	
16.00 – 18.00	Plenary: Restitution of Working Groups 1 and 2	
19.30	Reception hosted by the KFDA	

Friday, 16 June 2006		
09.00 – 10.30	Plenary: Finalization of draft report	
10.30 – 11.00	Coffee break	
11.30 – 12.30	Plenary: Finalization of draft report	
12.30 – 14.00	Lunch	
14.00 – 16.00	Adoption of Draft Report Closing remarks	
16.00 – 16.30	Coffee break	

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SUMMARY REPORTS OF WORKING GROUP DISCUSSIONS

WORKING GROUP 1: Aquaculture systems and production

(Prepared by Panos Christofilogiannis, Celia R. Lavilla-Pitogo and Donald Prater)

Introduction

Discussions about the use of antimicrobials in aquaculture require an understanding of the scope and diversity of aquaculture and the circumstances that affect the use of antimicrobials.

The goal of the section on Aquaculture Production and Utilization is to provide an overview of the current status of aquaculture as a component of the world's food supply, briefly discuss the types of species and prevalent culture systems employed in aquaculture, and finally discuss the use of therapeutics in aquaculture focusing on antimicrobials and their routes of administration. Having an understanding of this general information will help place the discussion about the risks and benefits of antimicrobial use in aquaculture in context.

Aquaculture is the production of certain species of aquatic animals and plants in confined systems. For the most part, aquatic species are cultured for use as human food, although other uses certainly exist. The culture of aquatic species occurs, by necessity, in aquatic environs. While this may seem a statement of the obvious, there are points upon which the culture of animals and plants in aquatic environments differ significantly from culture of animals in terrestrial environments. The administration of drugs and chemicals directly into culture water influences the speed and extent of exposure of non-target organisms, such as other vertebrates, algae, invertebrates and bacteria relative to administration in a land-based setting.

Aquaculture Production

As trends in global aquaculture production and utilization continue to grow the proportional contribution of wild-capture fisheries to the world's food supply is decreasing. Reflecting the growth of aquaculture, a diversity of aquatic species and types of culture systems have flourished over the past 50 years to meet the nutritional needs of both developed and developing countries. Nevertheless, 856 million people in the world are undernourished according to 2001-2003 FAO estimates. The need for high quality, nutritious sources of dietary protein is likely to fuel the demand for aquatic species well into the 21st century. The best source for describing the world's fisheries and aquaculture remains FAO's State of Fisheries and Aquaculture (SOFIA). Unless otherwise stated, production volumes and values for various countries, geographical regions, and aquatic species for this section of the report are taken from the FAO SOFIA Report for 2004.

Aquaculture provides an important component of the world's food supply and is growing relative to wild-capture fisheries and terrestrial animal agriculture. Global production of aquatic species (finfish, crustaceans, molluscs, and others) has grown significantly, increasing from 3.9% of total production by weight in 1970 to 27.1% in 2000 and to 32.4% in 2004.

Aquaculture has grown more rapidly than either capture fisheries or the terrestrial food animal production sector with average annual growth rates of 8.8%, 1.2% and 2.8% per cent respectively. Processed product from aquaculture has also outpaced population growth since 1970, with per capita supply increasing from 0.7 kg in 1970 to 7.1 kg in 2004, an average annual growth rate of 7.1%.

In 2004 the global production of food fish and aquatic plants was valued at over US\$ 70 billion on production of 59.4 million tons. This is compared with production of less than a reported one million tons in the early 1950s. In addition to increases in production there has also been an increase in the total value of the aquaculture crop as high-value species have come under intensive culture.

Aquaculture occurs in many regions of the globe but is most significant in the Asia-Pacific region, especially China. According to FAO, countries in the Asia-Pacific region accounted for 91.5% of the production volume and 80.5% of the value in 2004. Furthermore, of the world total, China produced 69.6% of the total volume and 51.2% of the total value of aquaculture production, a significant proportion of which is consumed domestically. Understanding the contribution of aquaculture product from the developing countries of the Asia-Pacific region is important when considering approaches to antimicrobial therapy.

In 2004 global aquaculture consisted of approximately 51% mariculture, 43% freshwater culture, and 6% culture in brackishwater environments. About two-thirds of brackishwater production consists of penaeid shrimps with finfish making up the difference. Freshwater culture consists largely of finfish which make up over 94%. Mollusks and aquatic plants on the other hand almost evenly make up most of the mariculture at 43% and 46%, respectively.

Species Diversity

Aquaculture is very diverse and there has been an increase in the number of cultured species and culture systems over the years. According to the FAO FishStat database, 442 different species have been cultured at sometime between 1950 and 2004. Since 1950 the number of species cultured has grown from 72 to 336 in 2004, for an average annual introduction of approximately five new species each year. The introduction of new species often results in the development of new or modified culture systems and a learning curve during which producers may experience increased disease outbreaks in species under intensive culture.

Production statistics can be examined by volume (tons of production) or by value (dollar value of production). Finfish are the top group by quantity or by value at 47% and 54% respectively. Aquatic plants are second in quantity at 23%, but only fourth in value at 9.7%. Crustaceans are fourth by quantity at 6%, but second by value at 20%. Molluscs are third by quantity or by value at 22% and 14%, respectively. Not well described by current FAO statistics is the production of cultured ornamental fish. Ornamental fish present challenges similar to other intensively reared species, including risk of disease and potential need for antimicrobial therapy. However, handling notwithstanding, they do not pose the same exposure profile as food fish with respect to human consumption.

Cyprinids are the most important finfish family by volume and total value. On an individual basis, their value is lower than some species, such as Atlantic salmon, which suggests that many farmed cyprinids are raised for local consumption, rather than for export. This highlights the important role of aquaculture in food security. It also highlights the situation in some developing countries where relatively low-value species are produced for domestic consumption and high-value species are produced for an export market, typically in developed

countries with significant regulation of the imported product. Production of a product for a highly-regulated market may influence the use of antimicrobial therapies for certain species.

After finfish, oysters are a distant second by volume at 4.6 million tons and are followed closely by kelps at 4.5 million tons. Crustaceans represented by penaeid shrimps and grapsid crabs have high total values relative to their production volumes and are another example of high value species.

Seafood Consumption

Global per capita seafood consumption has increased over the past four decades, from 9.0 kg in 1961 to an estimated 16.5 kg in 2003 according to FAO statistics. As nutritional standards have increased worldwide, particularly in developing countries, so has protein intake, rising from 65.1 grams in 1970 to 75.7 grams in 2003.

In recent years, fish has been widely recognized as a highly nutritious source of protein, essential fatty acids, micronutrients and minerals. In many countries, especially developing countries, the average per caput fish consumption may be low, but, even in small quantities; fish can have a significant positive impact in improving the quality of dietary protein by complementing the essential amino acids that are often present in low quantities in vegetable-based diets according to FAO.

During the last few years, major increases in the quantity of fish consumed originated from aquaculture, which in 2004 is estimated to have contributed 43% of the total amount of fish available for human consumption. Aquaculture production has pushed the demand and consumption for several high value species as shrimps, salmon and bivalves. During the last two decades, these species shifted from being primarily wild-caught to being primarily aquaculture-produced, with a decrease of their prices and a strong increase in their commercialization. Aquaculture has also a major role in terms of food security in several developing countries, particularly in Asia, for the significant production of some low-valued freshwater species, which are mainly destined to domestic consumption.

Culture Systems

Contributing to the diversity of aquaculture is the number of different culture systems employed to produce an increasing number of species. A wide variety of culture systems are employed to meet the production needs of the cultured species and maximize the resources available in the region. Each culture system has aspects that affect the production densities and risk for disease, as well as affect the ways in which antimicrobials are administered and handled with respect to uptake by the cultured species and excretion into the environment. In addition, economic factors may influence the predominant type of culture system in a particular region. For example, subsistence farmers and domestic producers may utilize predominantly extensive systems, particularly in China, Asia and developing countries, while producers for export, those producing high-value species, utilize more intensive systems. As economic efficiencies improve, there has been a trend towards an increase in the proportion of intensive systems.

While the current FAO reporting system for aquaculture works well for describing production and utilization, the classification system by environment creates a challenge for determining the relative importance of each culture system in the respective regions. However, the dominant system may be inferred for each region using the dominant species produced. Cyprinids are most likely produced in freshwater fishponds, salmons in sea cages, shrimps in

brackish water or marine ponds, and channel catfish in raceways or freshwater ponds. On the other hand marine bivalves are mostly produced using lines, racks and stakes and seaweeds are primarily produced using lines. By inference this would mean that freshwater fishponds, sea cages, lines and racks are all important in Asia, while sea cages are dominant in Europe. There are also land-based, industrial-type hatchery and nursery aquaculture production systems where temperature is controlled and where liquid oxygen may be used. These systems are energy intensive and are used primarily for grow-out for very high value products intended for niche markets. For example, this system is used for abalone culture in Australia, for tilapia culture for the live market, and for hybrid striped bass in the United States of America. The commercial aquaculture of marine finfish is expanding and likely to take place in more offshore locations than have traditionally been used. Cages developed specifically for offshore culture have been put into commercial use in recent years. More development in this area is envisioned.

Earthen pond and limited-flow culture systems are widely used throughout the world. Freshwater ponds are a principal system for the culture of cyprinids in Asia and channel catfish in the United States of America, while brackish water or marine ponds are the predominant system for shrimps. Ponds can be of any size, typically ranging from 0.2 ha (0.5 acre) to 8 ha (20 acres) with a depth of 1.0m to 2.0m. Ponds may be managed as extensive systems with low stocking densities and low nutrient input relying on natural sources of feed; as semi-intensive systems with supplemental feeding of artificial diets and a consequent increase in production; or as intensive systems with high stocking densities, large inputs of feed, and a higher level of monitoring and control to maintain appropriate water conditions. High stocking densities and reduced water quality are key factors associated with the potential for disease outbreaks, and are important in other culture systems as well. Pond culture systems are sensitive to environmental conditions particularly temperature.

Flow-through tanks and raceways. Salmonids and other coldwater species require access to clean, highly oxygenated water meaning that static pond water is not suitable for these species. Freshwater salmonids are grown in raceways or tanks with continuous water flow through. The simplest gravity fed system for trout farming includes earthen ponds, typically 30m x 10m x 1.5m, employing as a water source an adjacent stream. Circular tanks or concrete raceways represent a more intensive approach with higher water flow and at least 10-fold increased stocking densities. With a usual length of up to 100m, with a depth of 1m and width of 3m, raceways are segmented by fish screens or, depending on gradient, smaller splashdown raceways. Circular tanks with a diameter of 4m to 5m and a depth of 0.7m are made of concrete, fibreglass or coatings that resist erosion, prevent algal accumulation and employ water exchange of at least three times per hour. Water inlets are peripheral inducing a vortex action and self-cleaning properties, especially in slightly sloped bottom tanks.

Net pen and cage culture systems share the fundamental characteristic of utilizing an enclosure to rear aquatic species in open bodies of water. Net pens are the predominant marine culture system for salmonids in Norway, Scotland and Chile. Net pens vary from flexible net bags to semi-rigid with flexible internal construction to rigid boxlike structures. Net pen volumes range from 1000 m³ to over 20 000 m³ and are typically moored in natural bays or near-shore locations. Cages differ from net pens in that they are typically smaller and have rigid frames. Cages may be used in a variety of environments such as ponds, streams and coastal waters. When feeding fish in net pens or cages particular attention must be paid to sinking feed falling through the bottom of the cage or floating feed leaving the sides or top of the enclosure.

Recirculating systems are described as closed and semi-closed systems where some percentage of the total water volume is replaced on a continuous basis. Basic components include a settling chamber, a biological filter, and culture chambers (tanks, raceways). These systems typically require high-energy inputs and offer maximum control over culture conditions. Similarly, they offer a high degree of control over inputs into the system, such as feed and therapeutants, and outputs from the system, such as solid waste, effluent, and cultured fish. The addition of a specific biofilter adds a consideration to antimicrobial therapy in these systems. Antimicrobial therapy may require bypassing the filter and/or flushing the system.

Offshore farming is a term used to distinguish the location of this type of culture from near-shore or natural bays. Net pens or sea cages are used, but must be able to withstand conditions of being several miles away from shore, i.e. rough seas and infrequent onshore repairs, etc. Advantages of these systems include increased exchanges and dispersion of wastes and fewer aesthetic issues associated with near-shore farming. The technological feasibility is still being developed and is being encouraged by some governmental bodies. Issues associated with the use of antimicrobials still include exposure to non-target species but may be mitigated by the increased distances from shore.

Integrated systems and polyculture. Integrated aquaculture and polyculture describe a variety of systems in which agricultural crops, terrestrial livestock and aquatic species are cultured in such a manner as to maximize energy exchange from waste or byproducts, or derive some other benefit from the simultaneous culture of multiple species. Systems may be simple, such as the storage of irrigation water in aquaculture ponds, or much more elaborate in the number of species cultured and the level of integration. Specific issues are those of disease transmission and accumulation of toxic compounds. The use of antimicrobials in such systems is often complicated by the relatively free exchange of water and microorganisms within the system.

Use of Antimicrobials in Aquaculture

Antimicrobial use in cultured aquatic species has paralleled the growth of aquaculture over the last 50 years. As the proportion of intensive culture systems and the number of new species under culture has grown, so have the diversity of antimicrobial agents and the extent of their use. Factors influencing the risk of disease in intensive culture systems are well described and include high stocking densities and reduced water quality. However, sometimes overlooked is the fact that the number of new species introduced into culture also contributes to an increase risk of disease as a result of the learning curve experienced by culturists in developing efficient production systems. As the production systems become more refined the need for and the use of antimicrobials can be reduced by improvements in husbandry and alternate management tools such as the use of vaccines.

Constraining the use of antimicrobials in aquaculture is a variety of factors that include high cost, prohibited or uncertain regulatory status, infeasible routes of administration, poor absorption, toxicity, and environmental considerations. Nevertheless, the drive to minimize production losses and the relative availability of antimicrobial agents in certain regions has contributed to the use of antimicrobials in aquaculture. Not unlike human and terrestrial counterparts, bacterial resistance to antimicrobials has become widespread in aquaculture.

Antimicrobials are applied to aquatic species in their culture system. The ability to remove aquatic species from their culture system and treat them on an individual basis is often limited to high value individuals, such as broodfish or ornamental fish. Systems for applying

injections to multiple animals are limited to infrequent applications such as vaccines and are not routinely employed for antimicrobials on a production basis.

Although antimicrobial therapy should be guided by principles of disease diagnosis and rational chemotherapeutic selection and administration, empirical therapy and prophylactic use have caused concern for the development of antimicrobial resistance. Of particular concern is the potential for the development of resistant bacteria that could be transferred to humans through food handling and consumption.

The two most common routes of administration for antimicrobials in aquaculture are immersion therapy and medicated feed. Immersion therapy is commonly used for problems involving ectoparasites, and is used less often to treat bacterial diseases in juvenile stages. However, land-based hatcheries and tank systems, especially marine finfish and crustacean hatcheries, do use antibiotic baths. These usually last one to two hours, but more prolonged baths are not uncommon. This method is employed where the biomass is small, such as with fry, and when adequate oral therapy is impractical, as with larvae. Tank water volume is usually reduced, and consequently, the amount of drug required is reduced. The discharge of such treated water, however, poses an environmental consideration. A dip is a kind of immersion treatment that takes few seconds to minutes. A short bath is an immersion treatment that takes few hours to accomplish. A flush is a highly concentrated chemical solution that is allowed to enter at the water inlet and flow through quickly into the effluent pipe. A long bath is a treatment in which fish remain in the treatment solution for 12 hours or more. A flow-through is a treatment that is added at a constant rate through a metering device to give a consistent dose for the desired treatment time.

Medicated feeds are prepared by the addition of a small amount (premix) of the antimicrobial to a homogenized and extruded diet or sometimes sprayed or top-coated onto feed. The successful administration of a medicated feed is largely dependent on the level of feeding of the infected population. Sick fish tend to go off feed and palatability also becomes an issue with certain formulations. Correctly diagnosing a disease outbreak at an early stage and offering a palatable feed are important. Principles of clinical pharmacology such as the bioavailability of the drug, concentrations at which it accumulates in the host tissues, and the elimination rate should be taken into account with medicated feeds. The amount of uneaten food and drug remaining in faeces should be minimized.

Unfortunately, the availability of diagnostic services is limited in many developing countries and rational therapy based on identifying the specific pathogen followed by determining the most efficacious drug does not always occur. The proper use of antimicrobials is often compounded by poor or nonexistent product labeling.

Future Trends

There is likely to be an increase in the number of species cultured. There is a trend towards more intensive systems which will likely result in increased stocking densities and increased risk of disease. Although better management and husbandry of established species and culture systems is likely, there will continue to be challenges for the management and husbandry of newly-cultured species or newly-developed systems. There may be increased use of alternate therapies, particularly vaccination as technology improves. However, there will also be continued need for antimicrobials along with other therapeutic modalities. Harmonization of drug approval efforts could result in more approved products with better labeling including risk

mitigation strategies. Traceability and product labeling may decrease off label use and residues.

WORKING GROUP 2:

Animal health issues: towards a risk analysis of antimicrobial use in aquaculture

(Prepared by Victoria Alday, Benjamin Guichard, Peter Smith and Carl Uhland)

Introduction

An antimicrobial agent has never been developed specifically for an aquaculture application. Given the cost of drug development and licensing and the economics of aquaculture it is unlikely that any will be in the near future. The antimicrobial agents used in aquaculture are, therefore, those that have been developed for and are used to treat humans or other land-based animals. This raises the question of whether antimicrobial agent use in aquaculture can have a negative impact on the therapeutic value of these agents for human disease - and if this negative effect is evident, how big is it and what can be done to minimize it?

In addressing the risks to human health represented by the use of antimicrobial agents in aquaculture, three major problems have to be confronted. The first is related to the very diversity of aquaculture systems, the second is related to the paucity of information, and the third relates to the complexity of the exposure pathways involved.

Diversity

It is impossible to overstate the diversity of activities that must be included under the term "aquaculture".

Although in 2000, 29 species belonging to a number of different phyla accounted for 78% of global aquaculture production, the farming of an additional 180 different aquatic animal and plant species was also reported. This vast range of species is reflected in the diversity of culture systems used in aquaculture.

From the perspective of microbial ecology the diversity is just as great. Temperatures encountered in aquaculture can vary over at least a 30°C range and salinity can vary from 40 g/l to 0. The nutrient levels in aquaculture systems also vary over a wide range. Some systems operate with pure spring water whilst, at the other end of the spectrum, some involve the deliberate eutrophication of the water. Equally systems vary with respect to their exposure to bacteria present in human or animal wastes.

The socioeconomic environments within which aquaculture operates also vary over the full range found in the world. The bulk of aquacultural production occurs in Asia, often in LIFDC's where it plays a major role in meeting subsistence nutritional requirements, as a vital source of employment, profit and of foreign exchange earnings. Aquaculture is also practiced in the developed world where it is often run by sophisticated multinational companies. Thus, the scientific and technical infrastructure available to aquaculture producers and the regulatory environments within which they operate show wide variations.

Treating aquaculture, and therefore antimicrobial agents use in aquaculture, as a single category has the automatic result that only very broad generalizations can be made.

Paucity of information

Antimicrobial use

Amounts of antimicrobials used in aquaculture

In general it has been difficult to obtain accurate data on antimicrobial agent use in aquaculture. However, estimates can be offered for some European countries. In Norway, which has been collecting accurate statistics for some years, and in Sweden, recent estimates suggest that approximately 2 g of antimicrobials were used per tonne of aquaculture product. Data from the UK would suggest an aquaculture usage of 10-20 g/t and those from Denmark, France and Greece would indicate a slightly higher use of between 40 - 100 g/t. With respect to Canada and Chile, best estimates (157 g/t and >200 g/t respectively) would suggest that usage is higher than in most European countries. Data from Asia, where the vast majority of aquacultural production takes place, has been even more difficult to obtain. However, an indirect estimate of usage in Viet Nam would suggest a figure of 700 g/t. This might suggest that European data would provide a poor guide to usages in other countries.

Range of antimicrobials used in aquaculture

In countries such as those of Europe and northern America, where licensing and regulation of the use of antimicrobials are strictly enforced and where use is always under veterinary guidance, it would be typical that 2-4 agents would be available to aquaculture. Those most commonly licensed would be oxytetracycline, trimethoprim-sulfadiazine (or ormetoprim/sulfadimethoxine in American countries), oxolinic acid and/or flumequine, and florfenicol. It is probable that, in these countries, off-label use will only be involved in a small minority of administrations. In highly-regulated countries, low sales volumes and high cost of licensing have already resulted in companies deciding not to renew their licenses and to withdraw their compounds from the market, thereby further reducing the therapeutic option open to veterinarians to treat fish diseases.

This high degree of regulation occurs in countries that account for only a small percentage of world aquaculture production. In contrast, licensing, enforcement of regulations (where they exist) and use under veterinary guidance is less common in those countries that account for the vast bulk of world aquaculture production and an even greater proportion of antimicrobial agent use in aquaculture. The unregulated nature of use in these countries precludes any accurate identification of the agents used. It should also be noted that in many of these countries the lack of regulation also extends to the use of antimicrobials in human and veterinary medicine.

Rationale and style of administrations

In some systems antimicrobial agents are almost exclusively administered in feed; in others, administration via water is common. Again a wide variation is seen in the rationale for antimicrobial use. At one end of the spectrum antimicrobials are used only in response to epizootics and then only under veterinary prescription and after diagnosis and susceptibility tests have been performed. At the other end of the spectrum antimicrobials are used in an *ad hoc* manner and selection of agents is made based on price and availability in an unregulated market. It was the opinion of many with experience in the field that, in all countries, the use of antimicrobials was more common in small production units with no or low knowledge and advice in fish pathology and therapeutics.

Fate of antimicrobials

The extent and quality of the data on the fate of antimicrobial agents used in aquaculture again shows extreme variation. Adequate data is available for marine salmonid farms and these indicate that the distribution is local and transitory. In under-farm sediments, where the maximal concentrations occur, these may not reach levels capable of exerting selection for resistance. Concentration in the water bodies leaving farms are also unlikely to reach selective levels.

In contrast, little data is available concerning the fate of antimicrobials used in other aquacultural systems which are responsible for the vast majority of aquaculture production world-wide.

Selection exerted by antimicrobial use

There is clear evidence that the use of antimicrobials in aquaculture has been accompanied by the emergence of resistant variants of bacteria associated with fish disease. There is also ample evidence that, in these bacteria, the resistances may be encoded in plasmid located genes that can be transferred to terrestrial bacteria. Current evidence would indicate that the genes encoding resistance in aquatic bacteria are similar to those encountered in terrestrial bacteria.

There are also extensive data demonstrating that the presence of bacteria resistant to many antimicrobials occur with high frequencies in many aquatic environments. Evidence that antimicrobial use in aquaculture has exerted a selective pressure for the enrichment of resistance variants in terrestrial or aquatic bacteria present in the environment of farms is less convincing. The very few studies that have adequately addressed the complex methodological problems and that have included adequate controls provide contradictory evidence as to the extent of any selective pressure on these bacteria. Aquatic animals do not have a commensal intestinal microflora of the type encountered in land-based animals. This may account for the conflicting evidence as to whether there is even any selection for resistant variants in the intestines of fish receiving oral therapy.

At present, there are no data that demonstrate selective enrichment, in the environment of aquaculture facilities, of bacteria possessing resistance genes. Examination of scientific literature reveals a very significant shortage of data on the extent to which antimicrobial agents use in aquaculture result in the enrichment of bacteria possessing resistance to those agents.

Hazards and exposure pathways

The adverse health effects that might occur in humans as a result of antimicrobial use in aquaculture are those associated with residues in the food produced or with resistance in bacteria associated with human disease. Resistance in bacteria associated with human disease may arise either directly via enrichment for these bacteria in the aquaculture environment or indirectly via the enrichment for genes that encode such resistance and which may subsequently be transferred to bacteria associated with human disease.

Residues

The pathways by which antimicrobial residues in aquaculture products may pass to human are direct and for the purposes of risk analysis relatively easy to model. It should be noted that no case of an adverse reaction resulting from the consumption of aquacultural products contaminated with residues has ever been reported. It should also be noted that market forces

and pressure from retailers has had a major influence on reducing the presence of residues in fish traded in international markets.

Resistant bacteria

In contrast to the situation in land-based animals, bacteria capable of causing disease in humans via the oral route are rare in the aquaculture environment. The FAO/NACA/WHO Study Group (WHO, 1999) investigated the extent to which aquaculture products represented a vector of a number of potential human pathogens. They estimated that with respect to *Vibrio cholerae*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Listeria monocytogenes*, *Edwardsiella tarda*, *Salmonella* spp, other *Enterobacteriaceae* and *Campylobacter* spp the risks of disease transmission via aquaculture products were low. They also stated that confirmed cases of septicaemia and gastrointestinal disease caused by *V. vulnificus* following consumption of products from aquaculture have not been reported. *V. parahaemolyticus* is recognized as a major cause of gastroenteritis associated with the consumption of fish but current evidence suggests that there are differences between the sub-types of this species found in aquaculture and those found in human disease.

This evidence, which includes consideration of both pre-harvest and post-harvest contamination, suggests that the risks of disease resulting from the consumption of aquaculture products is low. The fact that most diseases of this type that do occur are self-limiting and would not, therefore, require antimicrobial therapy, further reduces the consequence of any enrichment for resistant variants that might have occurred as a result of aquacultural use of these agents.

A number of bacteria have been associated with diseases resulting from the handling of fish. These include, *Erysipelothrix rhusiopathiae*, *Mycobacterium marinum*, *Photobacterium damsela*, *Streptococcus iniae* and *Vibrio vulnificus*. In general, infections by these bacteria are rare and often associated with poor health in the host.

It is, however, possible that antimicrobial use in aquaculture might select for resistant variants of any of the bacterial groups identified above. In general there is a significant lack of data that can be used to investigate the significance of the risks to human health associated with such selection. In order to provide a qualitative assessment of these risks it is necessary to establish a series of appropriate exposure pathways. These pathways will be more complex than those developed for residues and will require the collection of a much wider range of information. However, only after the development of a consensus on the pathways will it be possible to specify the specific data that will be required to assess the risks.

Resistant genes

Our current understanding of bacteria suggests that gene exchange between members of different species is a regular occurrence. Thus it is possible that the enrichment, during aquacultural use of antimicrobials, of bacteria containing such genes may have an impact on the frequencies of these genes in bacteria associated with those human infections that require antimicrobial therapy.

It has been known for over 30 years that bacteria possessing resistance genes can be selected for by aquacultural use of antimicrobials and that such genes can, in laboratory experiments, be transferred to bacteria associated with human infections. What has never been established is whether such selection and transfer occurs in the natural world and, if it occurs, what is the

frequency of such transfers and what are the consequences for human health. As a consequence we are not in a position to provide even a qualitative assessment of the risk to human that is based on scientific data.

The central problem that has prevented any significant progress being made is the lack of any sophisticated theoretical understanding of the factors influencing gene flow in the bacterial world. Very serious consideration must be given to the possibility that gene ecology represents a self-regulating complex system and that linear, causal and mechanistic models may be of little value.

It is argued that in order to make any progress, attempts must be made to establish relevant exposure pathways. It is recognized that such pathways will be very complex and will involve developments of risk analysis frameworks into new and very difficult territories. It is recommended that systems biologists and those with experience of working with other complex systems should be included in any group charged with developing the necessary pathways.

Conclusions

The extreme diversity of aquaculture has the consequence that any attempt to analyse or assess the risks to human health associated with the use of antimicrobials in aquaculture can, if aquaculture is treated as a single activity, only produce very broad generalizations. These generalizations will have little meaning when any specific aspect of aquaculture is considered. Most importantly they will not provide the information that will allow the formulation of effective and relevant risk management strategies that can be followed in any specific situation.

The power of the available risk analysis frameworks can be applied only to problems that have been adequately and specifically defined. This would suggest that, at this stage, the most important task is to develop a set of criteria for prioritizing the various risks that can be identified. In this context a risk should be specified with respect to a number of parameters. The specific hazard and not a general hazard group should be identified. The aspect of the global aquaculture industry that is to be the focus of the investigation should also be specified. Here it will be necessary to specify the species farmed and the environmental conditions of the enterprises. In addition it will be necessary to identify the geographical area with respect to which the risk analysis is to be performed. In this sense the geographical area provides a proxy classification of the socioeconomic and scientific infrastructural of the aquaculture operation.

Earlier it was noted that, with respect to antimicrobial use in aquaculture, there is a serious lack of data. Even where data are available much of them are not relevant to the issues raised by risk analysis. The identification of specific risks and the exposure pathways associated with them represent the most effective way in which data requirements can be identified in sufficient detail to allow the collection, at last, of relevant information.

WORKING GROUP 3: Public health issues

(Prepared by Fred Angulo, Peter Collignon, Ole E. Heuer, Iddy Karunasagar and Hilde Kruse)

Antimicrobial use in aquaculture

Aquaculture is a steadily growing industry, covering a wide range of species and methods from simple traditional systems, where fish are reared in small ponds for domestic consumption, to intensive industrial-scale production systems. To control infectious diseases in aquaculture, the

same strategies as used in other areas of animal production are employed, including the application of antimicrobial agents. The most common fish infections treated with antimicrobials are skin ulcers and septicaemia.

The use of antimicrobials in aquaculture differs to how they are used in people and terrestrial animals. In aquaculture, antimicrobials are often added to the feed, which is then placed in the water where the fish are kept, or antimicrobials may be added directly to the water. These practices result in a selective pressure in the exposed environments (mainly water). Consequently, the use of antimicrobials in aquaculture results in a broad environmental application impacting a wide variety of bacteria.

Aquatic bacteria are not different from other bacteria in their responses to exposure to antimicrobials. Genetic mobility is just as common and widespread in this ecological environment as in others. Furthermore, there is overlap between the various ecological niches, including aquaculture and human environments, which means that bacteria and the resistance genes they contain may circulate between these different environments. Thus, addressing risks in relation to aquaculture requires a holistic approach.

Many antimicrobials used in human medicine are also applied in aquaculture. Table 1 summarizes the main antimicrobials that are used in aquaculture worldwide and their importance in human medicine as identified during the WHO Expert Consultation on Critically Important Antibacterial Agents for Human Medicine for Risk Management Strategies of Non-Human Use, in Canberra, Australia, in 2005 (WHO 2005).

Table 1: Major antimicrobial drugs (and classes) used in aquaculture

Drug (and class)	Administration	Importance of antimicrobial classes in human medicine
Amoxicillin (aminopenicillins)	Oral	Critically important
Ampicillin (aminopenicillins)	Oral	Critically important
Chloramphenicol (amphenicols)	Oral/bath/injection	Important
Florfenicol (amphenicols)	Oral	Important 1)
Erythromycin (macrolides)	Oral/injection/bath	Critically important
Streptomycin, neomycin (aminoglycosides)	Bath	Critically important
Furazolidone (nitrofurans)	Oral/bath	Important
Nitrofurantoin (nitrofurans)	Oral	Important
Oxolinic acid (quinolones)	Oral	Critically important 1)
Enrofloxacin (fluoroquinolones)	Oral, bath	Critically important 1)
Flumequine (fluoroquinolone)	Oral	Critically important 1)
Oxytetracycline, chlortetracycline, tetracycline (tetracyclines)	Oral/bath/injection	Highly important
Sulphonamides, (sulphonamides)	Oral	Important

N.B. These drug classes were defined in the report of the Canberra meeting. However, some of the individual drugs were not specifically mentioned as those drugs are not used in humans. Other antimicrobials in the same class, however, are used in humans. Resistance to all members of the class will result from their use if resistant bacteria develop.

Assessment of the risks associated with antimicrobial use in aquaculture

Hazard identification

The public health hazards related to antimicrobial use in aquaculture include the development and spread of antimicrobial resistant bacteria, the occurrence of antimicrobial residues in aquaculture products, and a negative impact on the environment.

Development and spread of antimicrobial resistant bacteria

Today, development and spread of antimicrobial resistance has become a global public health problem that is impacted by both human and non-human antimicrobial usage (OIE/FAO/WHO 2004a). It is generally acknowledged that any use of antimicrobial agents can select for the emergence of antimicrobial resistant microorganisms and further promote the dissemination of resistant bacteria and resistance genes (OIE/FAO/WHO 2004a). Furthermore, resistance neither respects phylogenetical, geographical nor ecological borders. Thus, use of antimicrobials in one ecological niche, such as in aquaculture, can have impact on the occurrence of antimicrobial resistance in another ecological niche, such as human medicine.

Antimicrobial resistant bacteria in aquaculture present a risk to public health owing to either:

- Development of acquired resistance in fish pathogens and other aquatic bacteria whereby such resistant bacteria can act as a reservoir of resistance genes from which genes can be further disseminated and ultimately end up in human pathogens (e.g. the spread of a resistance genes from *Aeromonas* spp. to *E. coli*). This can be viewed as an indirect spread of resistance from aquatic environments to humans caused by horizontal gene transfer.
- Development of acquired resistance in aquatic bacteria able to infect humans. This can be regarded as a direct spread of resistance from aquatic environments to humans.

Indirect spread of resistance by horizontal gene transfer

Development and spread of antimicrobial resistance as a consequence of exposure to antimicrobial agents is well documented in both human medicine and veterinary medicine. It is also well documented that fish pathogens and other aquatic bacteria can develop resistance as a consequence of antimicrobial exposure (Sørum 2006). Examples include *Aeromonas salmonicida*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Citrobacter freundii*, *Yersinia ruckeri*, *Photobacterium damsela* subsp. *piscicida*, *Vibrio anguillarum*, *Vibrio salmonicida*, *Photobacterium psychrophilum* and *Pseudomonas fluorescens*. For example *Aeromonas salmonicida*, which causes disease in fish of temperate and colder areas, easily develop resistance when exposed to antimicrobials.

Acquired sulfonamide resistance in *Aeromonas salmonicida* was reported in 1955 in USA, and in the 1960s multiresistant strains were observed in Japan. Later on, multiresistant *Aeromonas salmonicida* have been described by many countries in various parts of the world, and transferable resistance plasmids are commonly detected in these strains (Sørum 2006). Typical transferable resistance determinants among *Aeromonas salmonicida* are those conferring resistance to sulphonamide, tetracycline, trimethoprim, and streptomycin. The use of quinolones in aquaculture in the control of bacterial infections from the 1980s resulted in the development of quinolone resistance in strains of *Aeromonas salmonicida*. This resistance was mainly mediated by mutation in the gyrase A gene (*gyrA*). So far genes resulting in quinolone

resistance in bacteria associated with fish have not been shown to be transferable (Sørum 2006). Development of resistance by shrimp pathogens such as *Vibrio harveyi* due to exposure to antimicrobials has also been reported (Karunasagar et al., 1994). Resistance to norfloxacin, oxolinic acid, trimethoprim and sulphamethoxazole was found to be high in bacteria in mud samples from shrimp farming locations in Viet Nam, and *Bacillus* and *Vibrio* were predominant among bacteria resistant to antimicrobials (Lee et al., 2005). A high prevalence of resistance to sulphonamide in bacteria from shrimp hatcheries in India was reported by Otta et al (2001).

The fact that the bacteria responsible for infections in fish often belong to bacterial families that also cause infections in humans increases the probability of spread from aquaculture to humans. Several studies have demonstrated that plasmids harbouring resistance determinants are often transferable from fish pathogens and aquatic bacteria to not only other bacteria within the same genus, but also to *E. coli*. For example, multi-resistance plasmids have been shown to be transferable to *E. coli* from *Aeromonas salmonicida*, *Aeromonas hydrophila*, *Edwardsiella tarda*, *Citrobacter freundii*, *Photobacterium damsela* subsp. *piscicida*, *Vibrio anguillarum*, and *Vibrio salmonicida* (Sørum 2006). A large multi-resistance plasmid conferring resistance to six antimicrobials was shown to be transferable from *Vibrio cholerae* O1 to *A. salmonicida*, *A. hydrophila*, *V. parahaemolyticus*, *V. cholerae*, *V. anguillarum*, *Shigella* spp., *Salmonella* spp. and *E. coli* (Kruse 1995). Plasmids with varying resistance genes have been transferred in vitro from fish pathogens to human pathogens, including *Vibrio cholerae* and *Vibrio parahaemolyticus* (Angulo 1999). A 21kb plasmid coding for resistance to cephalothin that could be transferred to *E. coli* was isolated from *Vibrio* strains from shrimp ponds (Molina-Aja et al., 2002). Furushita et al. (2003) noted that genes coding for tetracycline resistance in fish farm bacteria and human clinical isolates in Japan showed high similarity suggesting that they may be derived from the same source. Further, in laboratory experiments, transfer of tetracycline resistance from marine strains of *Photobacterium*, *Vibrio*, *Altromonas* and *Pseudomonas* could be transferred to *E. coli* by conjugation suggesting that transfer of resistance from marine bacteria to bacteria associated with the human gut is possible.

The transfer of resistance plasmids between fish pathogens and other aquatic bacteria illustrates that these bacteria can act as reservoirs of antimicrobial resistance genes that can be further disseminated and ultimately reach human pathogens, and thereby add to the burden of antimicrobial resistance in human medicine.

Molecular characterization supports the suggestion that some of the antimicrobial resistance determinants in multiresistant *Salmonella* Typhimurium DT104 may have emerged, perhaps in Asia, in the early 1980s in aquaculture and were transferred horizontally to DT104 (Angulo et al. 2000). Tetracycline resistance in MR DT104 is due to a class G resistance gene. The class G resistance determinant is rare and had not previously been reported from *Salmonella* isolates. It was first identified in 1981 in tetracycline resistant isolates of *Vibrio anguillarum*. Chloramphenicol resistance in MR DT104 is encoded by a flo-like gene that confers resistance to both chloramphenicol and florfenicol. Flo was first identified in *Pasteurella piscicida*, the causative agent of pseudotuberculosis, a common disease of marine fish in Asia. Florfenicol was evaluated as a therapeutic agent in fish in the early 1980s. Kim and Aoki (Kim E.H., 1994) reported the emergence of florfenicol resistant strains of *Pasteurella piscicida* due to the acquisition of transferable resistance plasmids containing the flo-gene, in addition to other antimicrobial resistance marker genes (ampicillin, kanamycin, sulphonamides, tetracycline). Furthermore, nucleotide sequence analysis of the DNA region in MR DT104 containing the florfenicol resistance gene and two tetracycline resistance genes showed a 94% similarity to a sequence found in a plasmid from *P. piscicida* (Sørum 2006). In bovine *E. coli*, a florfenicol

resistance gene with 98% homology is relatively common. These molecular characterizations strengthen the evidence that antimicrobial resistance genes selected for in the aquaculture ecosystems can be transmitted to human bacteria.

Direct spread of resistance

Aquatic environments can be a source of resistant bacteria that can be directly transmitted to, and cause infections in, humans, and, owing to resistance traits, may result in treatment failures. Such direct spread of resistance from aquatic environments to humans may involve human pathogens such as *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Vibrio vulnificus*, *Shigella* spp. and *Salmonella* spp. or opportunistic pathogens such as *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Edwardsiella tarda*, *Streptococcus iniae* and *E. coli*. The occurrence of resistant *Salmonella* spp. and *E. coli* in aquatic environments is a result of contamination from human, animal or agricultural environments. The spread to humans of resistant human pathogenic or opportunistic bacteria may be through direct contact with water or aquatic organisms, through drinking water or through the handling or consumption of aquaculture products. Such infections are in general relatively uncommon. Infections with opportunistic bacteria are more likely to occur in those with impaired immune systems.

Occurrence of antimicrobial residues

Antimicrobial usage in aquaculture can result in residues of antimicrobials in aquaculture products. Such antimicrobial residues can present a hazard to public health if the consumer becomes exposed to the residues, either through the consumption of aquaculture products containing residues or by the handling of products containing residues. In addition, antimicrobial residues in aquaculture products present a major perceived risk as many consumers have concerns about the possibility of residues of antimicrobials in aquaculture products.

Hazard characterization

Antimicrobial resistance

The consequences of antimicrobial resistance in bacteria causing human infections include: (1) increased number of infections, (2) increased frequency of treatment failures and increased severity of infection, and finally (3) increased costs to society associated with disease (OIE/FAO/WHO 2004a).

(1) Increased number of infections

The use of antimicrobial agents in humans disturbs the microflora of the intestinal tract, placing such individuals at increased risk of certain infections. Individuals taking an antimicrobial agent, for any reason, are therefore at increased risk of becoming infected with pathogens resistant to the antimicrobial agent. This effect has been demonstrated in case-control studies of persons infected with antimicrobial-resistant *Salmonella* in which persons exposed to antimicrobial agents for unrelated reasons, such as treatment of an upper respiratory tract infection, are at increased risk of infection with *Salmonella* that is resistant to the antimicrobial agent. This increased risk can be expressed in the form of an “attributable fraction”, which is defined as the proportion of *Salmonella* infections that would not have occurred if the *Salmonella* were not resistant (or if the person had not been taking the antimicrobial agent for the unrelated reason).

It is reasonable to assume that the same phenomenon as demonstrated for Salmonella can occur with other resistant human pathogens, which resistance might have originated in aquaculture; that antimicrobial treatment put the patient at risk for infection with such resistant pathogens.

(2) Increased frequency of treatment failures and increased severity of infection

Increased frequency of treatment failures and increased severity of infection as a result of antimicrobial resistance may be manifested by prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, or increased mortality (OIE/FAO/WHO 2004a). Prolonged duration of illness has been demonstrated in case-control studies of fluoroquinolone-resistant Campylobacter (Smith et al, 1999; Neimann et al, 2003). Prolonged duration of illness has also been demonstrated among persons infected with Salmonella Typhi resistant to the quinolone nalidixic acid and then treated with fluoroquinolones. The association between an increased frequency of antimicrobial resistance Salmonella and an increased frequency of hospitalization has been demonstrated in several studies.

It is reasonable to assume that the same phenomenon as demonstrated for Salmonella and Campylobacter can occur with other resistant human pathogens, where resistance might have originated in aquaculture, and that such resistant pathogens may cause treatment failures and increased severity of disease, including an increased fatality rate.

Antimicrobial residues

Antimicrobial residues present a hazard to public health as these can cause serious illness. Drug allergies are mediated by a number of different immunological mechanisms that includes type 1 immediate immune response mediated through IgE. Symptoms include anaphylaxis, skin-rashes, urticaria and angioedema. Penicillin is the most commonly implicated antimicrobial in adverse reactions from foodborne residues, causing penicillin hypersensitivity or skin disease unrelated to penicillin allergy. Penicillin residues as low as 5-10 IU are capable of producing allergic reactions in previously sensitized persons (Sundlof 1993). Chloramphenicol presents a particular threat to human health as it can cause a dose-independent aplastic anemia in humans, and idiosyncrasy, which can be potentially induced by low concentrations of chloramphenicol in foods.

Exposure assessment

Prevalences of antimicrobial resistance in aquatic bacteria / fish bacteria

Quinolones such as oxolinic acid were extensively used in aquaculture against Aeromonas salmonicida infections from the end of the 1980s until effective vaccines were introduced in the early 1990s (Sørum 2006). In that period, Aeromonas salmonicida with high MIC for quinolones were detected in all areas where furunculosis was endemic in salmon farming. An increase in the prevalence of oxolinic acid resistant Acinetobacter spp. in a stream that received the effluent from a freshwater trout farm following treatment with oxolinic acid-medicated feed was reported by Guardabassi et al, 2000. They observed an increase, at least 10-fold, in the MIC-values for ciprofloxacin for the oxolinic acid-resistant isolates.

Antimicrobials are commonly used in shrimp farming to prevent or treat disease outbreaks but there is little published documentation on details of usage patterns. A study, conducted in 2003

(Graslund et al.2003), showed that a large proportion of shrimp farmers along the Thai coast used antimicrobials in their farms. Of the 76 farmers interviewed, 74% used antimicrobials in shrimp pond management. Most farmers used them prophylactically, some on a daily basis. At least 13 different antimicrobials were used. The authors concluded that a more restrictive use of antimicrobials could have positive effects for the individual farmer and simultaneously decrease impacts on regional human medicine and adjacent coastal ecosystems.

Although data are limited on antimicrobial use in Asia, available evidence indicate that countries in Asia with large aquaculture sectors use very large amounts of antimicrobials in aquaculture often without veterinary or other professional supervision, and often purchase directly from drug company salespersons without regulatory oversight. In contrast, available evidence indicates that in Europe and North America, use of antimicrobials in aquaculture is well regulated.

In a study of ready-to-eat shrimp (Dura N 2005), 13 brands from four countries were obtained from local grocery stores. A total of 1564 isolates representing 162 bacterial species were recovered during screening of resistance to 10 antimicrobials. 42% of the isolates and 81% of the species had acquired resistance to antimicrobials. Numerous resistant human pathogens were isolated, including *Escherichia coli*, *Enterococcus* spp., *Salmonella*, *Shigella flexneri*, *Staphylococcus* spp., and *Vibrio* spp. Ready-to-eat shrimp is sold with instructions to thaw the product before serving and without the need for cooking, which is likely to result in consumer exposure to antimicrobial resistant bacteria. The authors concluded that widespread trade of this product provides an avenue for international dissemination of antimicrobial resistant pathogens.

Antimicrobial residues

The public health risk associated with antimicrobial residues depends on the quantity of the antimicrobial encountered or consumed, i.e. the exposure. In general, the lower the exposure, the lower the risk. In a FAO/OIE/WHO consultation on scientific issues related to non-human usage of antimicrobials held in Geneva, in December 2003, it was concluded that residues of antimicrobials in foods, under present regulatory regimes, represents a significantly less important human health risk than the risk related to antimicrobial resistant bacteria in food. The use of water and food as the administration route helps to obtain a uniform dose and avoid high localized concentration that might arise from use of injection. In most countries where antimicrobials are licensed for use in aquaculture, withdrawal times that ensure safety to the consumers are set. Non-compliance with these withdrawal times presents a risk to public health.

Risk characterization

The greatest risk to public health associated with antimicrobial use in aquaculture is the development of a reservoir of transferable resistance genes in fish pathogens and other aquatic bacteria. From these bacteria such genes can disseminate by horizontal gene transfer to other bacteria and ultimately reach human pathogens. Horizontal gene transfer to human pathogens may occur in the aquaculture environment, in the food chain, or in the human intestinal tract. When human pathogens are antimicrobial resistant this can cause treatment problems. The risk of horizontal gene transfer from fish pathogens and other aquatic bacteria ultimately to human pathogens is considered significant and of large magnitude. Therefore efforts are needed to prevent such development and spread of resistance genes.

The second greatest risk associated with antimicrobial use in aquaculture is the development of resistance in aquatic bacteria that are pathogenic for people and these resistant pathogenic bacteria are ultimately transferred to humans.

In contrast to aquaculture, in terrestrial food producing animals (cattle, chickens, pigs, turkeys), transfer of resistant pathogenic bacteria, such as Salmonella, to humans is a more important risk than horizontal gene transfer.

Antimicrobial residues under current regulatory regimes represent a smaller, but still significant public health risk. It is important that efforts are made to ensure that regulations that prevent residues are complied with and enforced.

Risk management options

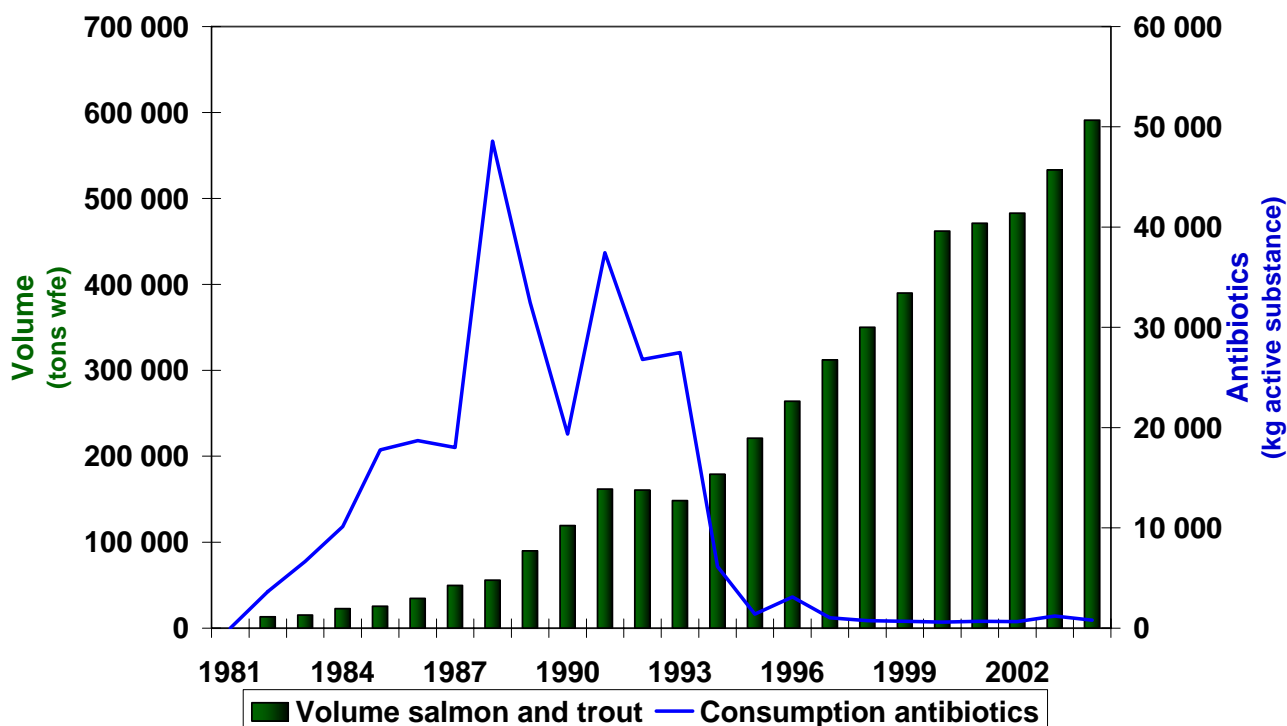
Prevention and control of infectious diseases in aquaculture

The most effective means to prevent development and spread of antimicrobial resistance is to reduce the need for antimicrobial treatment (Haastein 2000). The main components of disease prevention and control may be summarised as follows:

- legal basis for disease control in aquatic animals;
- highly qualified personnel at the aquaculture, laboratory and administrative level;
- stocking programmes and management practices to avoid disease outbreaks;
- disease prevention techniques to avoid the introduction of pathogens;
- control measures if disease occurs;
- eradication of certain pathogens from a facility and, if possible, from wild stocks.

An important measure in relation to disease prevention is the introduction of vaccines. Today, vaccines are available for many of the major infectious disease agents in aquaculture, and by the application of such vaccine the need for antimicrobials can be reduced substantially. In Norway, introduction of effective vaccines as well as improved health management had a major impact on antimicrobial consumption. The annual usage of antimicrobial agents in farmed fish declined by 98% from 1987 to 2004 (Figure 1).

Figure 1. Antimicrobial Usage vs Salmon and Trout Production in Norway



Regulatory control of antimicrobial usage

Countries should have a regulatory approval and control system for all antimicrobial agents and products containing antimicrobial agents used in animals, including aquaculture. Such a system could include, but not be limited to, listing of all available antimicrobial agents in the country and an approval mechanism. A pre-licensing safety evaluation of antimicrobials to be used in aquaculture with consideration of potential resistance to antimicrobials used in human medicine is important. Data show that when there is no regulatory control of antimicrobial use in aquaculture, farmers tend to use any antibiotic they might obtain (Hernandez 2005). It is recommended that antimicrobial usage, also in aquaculture, be under obligatory prescriptions.

Implementation of prudent use guidelines

Development and implementation of guidelines on prudent use of antimicrobials to veterinarians and other professionals prescribing antimicrobials as well as to those working in the aquaculture industry is essential. The WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (Global Principles) provide a framework of recommendations to reduce the overuse and misuse of antimicrobials in food animals for the protection of human health. The Global Principles were developed with the participation of FAO and OIE, as part of a comprehensive WHO Global Strategy for the Containment of Antimicrobial Resistance and are available at http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm

Monitoring of antimicrobial usage and antimicrobial resistance

An important component in the management of antimicrobial resistance is the implementation of monitoring of antimicrobial usage and antimicrobial resistance at the national level (WHO Global Principles). This applies also to aquaculture. Monitoring of antimicrobial usage and antimicrobial resistance provide important data for the identification of resistance problems and contributing factors for the development and spread of this resistance at a national and local level. Such data can also be used at the international level. Monitoring of antimicrobial usage and resistance serve many purposes including:

- documentation of the situation;
- identification of trends;
- linkage of antimicrobial usage and antimicrobial resistance;
- basis for risk assessment;
- basis for interventions;
- evaluation of effectiveness of measures implemented;
- basis for focused and targeted research;
- follow-up on compliance with regulation.

International and interdisciplinary cooperation

In order to improve and encourage work at the national level in regard to prevention and control of infectious disease in aquaculture, regulatory control of antimicrobial usage, implementation of prudent use guidelines, monitoring of antimicrobial usage and antimicrobial resistance, international and interdisciplinary cooperation is essential. The leadership of international organizations such as FAO, OIE and WHO is crucial.

Capacity building

There is a need to support and assist developing countries in their efforts regarding:

- implementation of preventive measures (hygiene, environmental conditions, vaccines);
- implementation of prudent use guidelines;
- regulatory control of antimicrobial usage;
- monitoring of antimicrobial use and antimicrobial resistance.

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**WHO GLOBAL PRINCIPLES FOR THE CONTAINMENT OF
ANTIMICROBIAL RESISTANCE IN ANIMALS INTENDED FOR FOOD**

**Report of a WHO Consultation with the participation of the Food and Agriculture
Organization of the United Nations and the Office International des Epizooties
Geneva, Switzerland, 5-9 June 2000**

Full report available at :

http://www.who.int/emc/diseases/zoo/who_global_principles/index.htm).

Purpose

To minimize the negative public health impact of the use of antimicrobial agents in food-producing animals while at the same time providing for their safe and effective use in veterinary medicine.

General

National governments should adopt a proactive approach to reduce the need for antimicrobials in animals and their contribution to antimicrobial resistance and to ensure their prudent use (including reducing overuse and misuse), as elements of a national strategy for the containment of antimicrobial resistance.

Relevant authorities should develop strategies that reduce the actual and potential risk to public health from antimicrobial-resistant bacteria and resistance genes, prolong the efficacy of veterinary antimicrobial products, ensure the maintenance of animal health, and establish systems for controls and interventions to ensure compliance with the developed strategies and regulations on the use of antimicrobials.

Responsibilities of regulatory and other relevant authorities.

A. Pre- and post-approval

Decisions concerning the licensing of veterinary antimicrobial substances should consider the impact on human health of antimicrobial resistance developing in food animals in which antimicrobials have been used.

No antimicrobial should be administered to animals unless it has been evaluated and authorized for such use by relevant authorities. Exceptionally, where no antimicrobial drug for use in a species or for a specific indication is authorized, or an authorized product is demonstrated to be no longer effective, then a product authorized for another indication or other species may be used under direct supervision of a veterinarian. However, relevant authorities which regulate extra label use of antimicrobials in food animals should consider restricting such use of those drugs deemed highly important in human medicine.

The authorization of veterinary antimicrobial products should take account of data on antimicrobial resistance among relevant bacterial strains and should ensure that recommended dosages are optimal for therapy, taking into consideration pharmacokinetics, clinical efficacy, residues, and, if available, other relevant data in order to minimize the development of

resistance. Existing product labelling should also be reviewed, when necessary, by regulatory authorities to ensure that the recommended dose and duration of use are consistent with current knowledge of efficacy, antimicrobial resistance, pharmacokinetics, pharmacodynamics and prudent use.

A risk-based evaluation of the potential human health effects of all uses of antimicrobial drugs in food producing animals should be conducted, including currently approved products. In the evaluation of currently approved products, priority should be given to those products considered most important in human medicine. Characterization of the risk should include consideration of the importance of the drug or members of the same class of drug to human medicine, the potential exposure to humans from antimicrobial-resistant bacteria and their resistance genes from food animals, as well as other appropriate scientific factors. Those antimicrobials judged to be essential for human medicine should be restricted and their use in food animals should be justified by culture and susceptibility results.

Decisions regarding registration of antimicrobials for use in food animals should be based on scientific data and, unless otherwise justified, should include the potential rate and extent of resistance in relevant bacteria associated with the proposed use in food animals in the pre-approval evaluation.

Post-approval surveillance is indispensable and surveillance of resistance to antimicrobials belonging to classes considered important in human medicine should be closely monitored so as to be able to detect emergence of antimicrobial resistance in time to allow corrective strategies to be implemented as part of an efficient post-licensing review.

Post-approval surveillance of antimicrobial resistance should include identification of the appropriate bacteria and methods of collection. Relevant antimicrobials to be included in such post-approval surveillance programmes should be guided by a risk-based priority list under the direction of the relevant authority. The methods and data should be made publicly available. Such surveillance may be carried out with the participation of the veterinary pharmaceutical industry.

Epidemiological and/or experimental investigations to identify risk factors may be needed if resistance increases above levels of concern, and proportionally incremental mitigation strategies^{*}, such as education, infection control, labelling changes, changes in dosing and duration of use, should then be implemented. If, and when the ongoing assessment of the risk demonstrates it to be unacceptable, withdrawal of an antimicrobial for veterinary use from the market should be considered.

Relevant authorities should ensure that all antimicrobials for disease control in animals are classified as prescription-only medicines unless, under exceptional circumstances, veterinary advice is not available and alternative means of disease control must be facilitated. Under such exceptional circumstances, relevant authorities should take steps to ensure that veterinary advice becomes available in the future.

B. Quality/Manufacturing

Antimicrobial products, including generic products, should be manufactured in accordance with the current good manufacturing practices (GMP) and following the specifications laid out

^{*} increasingly strict measures proportional to the risk identified

in the licensing application by the relevant authorities. Relevant authorities that lack the necessary resources to evaluate product applications should provide for alternative mechanisms, such as third party certification, to ensure safe, effective and quality products are licensed for use.

C. Distribution/Sales/Marketing

Enforcement policies should be designed to ensure compliance with laws and regulations pertaining to the authorization, distribution and sale, and use of antimicrobials. They should aim at preventing the illicit manufacture, importation, and sale of antimicrobials, and at controlling their distribution and use.

Special attention should be paid to the distribution and sale of counterfeit, sub-potent and misbranded veterinary antimicrobials. Enforcement action should be taken to stop such distribution and sale by relevant authorities, in coordination with the exporting country, if appropriate.

Relevant authorities should ensure that all antimicrobials for animal use should be supplied only through authorized outlets, such as pharmacies on veterinary prescription, veterinary practices and feed mills, in the case of materials used in animal feeding stuffs.

If sufficient evidence exists that profit from the sale of antimicrobials negatively impacts on prescribing practices, appropriate countermeasures should be taken to ensure prudent use.

The advertising and promotion of animal health products should comply with national guidelines and codes of practice. Commercial promotion of prescription-only antimicrobial products should be directed only to veterinary professionals.

D. Antimicrobial growth promoters

Use of antimicrobial growth promoters that belong to classes of antimicrobial agents used (or submitted for approval) in humans and animals should be terminated or rapidly phased-out in the absence of risk-based evaluations. The termination or phasing-out should be accomplished preferably by voluntary programmes of food animal producers, but by legislation if necessary.

Risk-based evaluations of all antimicrobial growth promoters should be continued. Characterization of the risk may include consideration of the present and potential future importance of the drug to human medicine, its selection of resistance, the potential exposure to humans from resistant bacteria from food animals, as well as other appropriate scientific factors.

Surveillance of antimicrobial resistance and antimicrobial usage

Data generated from the surveillance of antimicrobial resistance and antimicrobial usage should play a key role in the development of national policies for the containment of antimicrobial resistance. These data are also essential in the pre- and post-licensing process and in the development of treatment guidelines for veterinary use.

A. Surveillance of antimicrobial resistance

Programmes to monitor antimicrobial resistance in animal pathogens, zoonotic agents (for example, *Salmonella* spp. and *Campylobacter* spp.), and bacteria known to be indicators of antimicrobial resistance (for example, *Escherichia coli* and *Enterococcus faecium*) should be

implemented on bacteria from animals, food of animal origin and humans. Veterinarians, medical doctors, authorities and other stakeholders should be kept regularly informed about the surveillance results and trends. Antimicrobial susceptibility testing should be performed according to standardized methods using appropriate quality control, and be reported quantitatively to allow comparison of results.

B. Surveillance of antimicrobial usage

Relevant authorities should establish systems to determine the amounts of antimicrobials given to food animals.

Information on the amounts of antimicrobials given to food animals should be made publicly available at regular intervals, be compared to data from surveillance programmes on antimicrobial resistance, and be structured to permit further epidemiological analyses.

Prudent use of antimicrobials

A. Guidelines on prudent use

The strategic aim of policies expressed in guidelines should be to provide advice on optimal therapeutic effect and/or protection of animals at risk and on the control of antimicrobial resistance in animal and zoonotic bacteria.

Guidelines on the prudent use of antimicrobials in animals should be readily accessible, developed with multidisciplinary involvement, subject to peer review, compatible with existing regulations, and should be evaluated and revised at regular intervals.

Locally-derived species-specific treatment guidelines should include a list of antimicrobials for conditions commonly presenting in clinical practice and offer a rational treatment choice based on scientific data and knowledge, the disease and resistance situation, practical experience and human health concerns. If several antimicrobials can be used, guidelines should make recommendations on different antimicrobials to be used. However, the clinical experience and judgement of the practitioner should determine the final choice.

B. Responsibilities of veterinarians and/or producers

For each treated animal or group of animals a health record should be kept to support the choice of empirical therapy. The record should include:

- data on antimicrobial use;
- previous antimicrobial susceptibility test results; and/or
- previous treatment outcomes.

Veterinarians should continuously evaluate their prescribing practices. This would be based on information such as the main indications and types of antimicrobials used in different animal species and be evaluated in relation to available data on antimicrobial resistance and current use guidelines.

Veterinarians should prescribe antimicrobials only for animals under their direct care. Veterinarians are expected to have examined clinically affected animals, or to be familiar with production practices on the farm and to have developed a written treatment protocol, prior to prescribing medication.

Antimicrobials should be prescribed only when indicated, using antibiotics directed against the causative agent/s, given in optimal dosage, dosage intervals and length of treatment to ensure maximum concordance with the treatment regimen.

It is the responsibility of the producers to ensure that production systems promote animal health and welfare. Antimicrobial usage, if necessary, should always be a part of, not a replacement for, an integrated animal health programme. Such a programme is likely to involve hygiene and disinfection procedures, bio-security measures, management alterations, changes in stocking rate, vaccination and other relevant components.

Veterinarians together with producers should be jointly responsible for the health of animals on the farm. Veterinarians and producers should agree on policies and protocols on preventive strategies, health and treatment programmes and veterinary involvement in ongoing animal health management. These policies and protocols should comply with prudent use principles, good farming practice, and quality assurance programmes.

Prophylactic use of antimicrobials

Use of antimicrobials for prevention of disease can only be justified where it can be shown that a particular disease is present on the premises or is likely to occur. The routine prophylactic use of antimicrobials should never be a substitute for good animal health management.

Prophylactic use of antimicrobials in control programmes should be regularly assessed for effectiveness and whether use can be reduced or stopped. Efforts to prevent disease should continuously be in place aimed at reducing the need for the prophylactic use of antimicrobials.

Education and training

Veterinary undergraduate, postgraduate and continuing education should be evaluated to ensure that preventive medicine, prudent antimicrobial use and antimicrobial resistance are given high priority.

Ongoing education strategies should be developed by entities such as professional associations, relevant authorities, appropriate international organizations and/or educational institutions to provide relevant professional bodies and stakeholders with appropriately targeted information about infections, the role and benefits of prudent antimicrobial use and the risks of inappropriate use. All relevant stakeholders including the veterinary pharmaceutical industry and public health sectors should be encouraged to support this effort.

Continuous evaluation of the effectiveness of educational strategies for prudent use should be conducted.

Education strategies emphasizing the importance and benefits of prudent use principles must be developed and implemented to provide relevant information on antimicrobial resistance for producers and stakeholders. Emphasis must also be given to the importance of optimizing animal health through implementation of disease prevention programmes and good management practices.

The public should be informed of the human health aspects of antimicrobial use in food animals, so that they can support efforts to control antimicrobial resistance.

Research

Stakeholders should identify research priorities to address public health issues of antimicrobial resistance from antimicrobial use in food animals. Governments, universities, research foundations and industry should give high priority to supporting research in these areas.

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

(International Animal Health Code - 2006 APPENDIX 3.9.3.)

Article 3.9.3.1.

Purpose

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

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

Article 3.9.3.2.

Objectives of prudent use

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

1. maintain the efficacy of *antimicrobial agents* and to ensure the rational use of antimicrobials in animals with the purpose of optimising both their efficacy and safety in animals;
2. comply with the ethical obligation and economic need to keep animals in good health;
3. prevent, or reduce, as far as possible, the transfer of micro-organisms (with their resistance determinants) within animal populations;
4. maintain the efficacy of *antimicrobial agents* used in food-producing animals;
5. prevent or reduce the transfer of resistant micro-organisms or resistance determinants from animals to humans;
6. maintain the efficacy of *antimicrobial agents* used in human medicine and prolong the usefulness of the antimicrobials;
7. prevent the contamination of animal-derived food with antimicrobial residues that exceed the established maximum residue limit (MRL);
8. protect consumer health by ensuring the safety of food of animal origin with respect to residues of antimicrobial drugs, and the ability to transfer antimicrobial drug resistant micro-organisms to humans.

Article 3.9.3.3.

Responsibilities of the regulatory authorities

1. Marketing authorisation

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

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

The pharmaceutical industry has to submit the data requested for the granting of the marketing authorisation. The marketing authorisation is granted only if the criteria of safety, quality and efficacy are met. An assessment of the potential risks and benefits to both animals and humans resulting from the use of *antimicrobial agents* in food-producing animals should be carried out. The evaluation should focus on each individual antimicrobial product and the findings not be generalised to the class of antimicrobials to which the particular active principle belongs.

Guidance on usage should be provided for all dose ranges or different durations of treatment that are proposed.

3. Market approval

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

4. Registration procedures

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

- a. check the efficacy of administrative controls on the import of these VMPs;
- b. check the validity of the registration procedures of the exporting and manufacturing country as appropriate;
- c. develop the necessary technical co-operation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

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

5. Quality control of antimicrobial agents

Quality controls should be performed:

- a. in compliance with the provisions of good manufacturing practices;
- b. to ensure that analysis specifications of antimicrobial agents used as active ingredients comply with the provisions of approved monographs;
- c. to ensure that the quality and concentration (stability) of antimicrobial agents in the marketed dosage form(s) are maintained until the expiry date, established under the recommended storage conditions;
- d. to ensure the stability of antimicrobials when mixed with feed or drinking water;
- e. to ensure that all antimicrobials are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy.

6. Assessment of therapeutic efficacy

a. Preclinical trials

i. Preclinical trials should:

- establish the range of activity of antimicrobial agents on both pathogens and non-pathogens (commensals);
- assess the ability of the antimicrobial agent to select for resistance *in vitro* and *in vivo*, taking into consideration pre-existing resistant strains;
- establish an appropriate dosage regimen necessary to ensure the therapeutic efficacy of the antimicrobial agent and limit the selection of antimicrobial resistance. (Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal.).

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

- spectrum of activity and mode of action;

- minimum inhibitory and bactericidal concentrations;
 - time- or concentration-dependent activity or co-dependency;
 - activity at the site of infection.
- iii. The dosage regimens allowing maintenance of effective antimicrobial levels should be established by pharmacokinetics. The following criteria should be taken into account:
- bio-availability according to the route of administration;
 - concentration of the antimicrobial at the site of infection and its distribution in the treated animal;
 - metabolism that may lead to the inactivation of antimicrobials;
 - excretion routes.

Use of combinations of antimicrobial agents should be scientifically supported.

b. Clinical trials

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

- i. diversity of the clinical cases encountered when performing multi-centre trials;
- ii. compliance of protocols with good clinical practice, such as Veterinary International Cooperation on Harmonisation (VICH) guidelines;
- iii. eligibility of studied clinical cases, based on appropriate criteria of clinical and bacteriological diagnoses;
- iv. parameters for qualitatively and quantitatively assessing the efficacy of the treatment.

7. Assessment of the potential of antimicrobials to select for resistance

Other studies may be requested in support of the assessment of the potential of antimicrobials to select for resistance. The party applying for market authorisation should, where possible, supply data derived in target animal species under the intended conditions of use.

For this the following may be considered:

- a. the concentration of active compound in the gut of the animal (where the majority of potential food-borne pathogens reside) at the defined dosage level;
- b. the route and level of human exposure to food-borne or other resistant organisms;
- c. the degree of cross-resistance within the class of antimicrobials and between classes of antimicrobials;
- d. the pre-existing level of resistance in the pathogens of human health concern (baseline determination) in both animals and humans.

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

- a. When setting the acceptable daily intake (ADI) and MRL for an antimicrobial substance, the safety evaluation should also include the potential biological effects on the intestinal flora of humans.
- b. The establishment of an ADI for each antimicrobial agent, and an MRL for each animal-derived food, should be undertaken.
- c. For each VMP containing antimicrobial agents, withdrawal periods should be established in order to produce food in compliance with the MRL, taking into account:

- i. the MRL established for the antimicrobial agent under consideration;
 - ii. the composition of the product and the pharmaceutical form;
 - iii. the target animal species;
 - iv. the dosage regimen and the duration of treatment;
 - v. the route of administration.
 - d. The applicant should provide methods for regulatory testing of residues in food.
9. Protection of the environment

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

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

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

- a. active ingredient and class;
 - b. pharmacological properties;
 - c. any potential adverse effects;
 - d. target animal species and age or production category;
 - e. therapeutic indications;
 - f. target micro-organisms;
 - g. dosage and administration route;
 - h. withdrawal periods;
 - i. incompatibilities;
 - j. shelf-life;
 - k. operator safety;
 - l. particular precautions before use;
 - m. particular precautions for the proper disposal of un-used or expired products;
 - n. information on conditions of use relevant to the potential for selection of resistance.
 - o.
11. Post-marketing antimicrobial surveillance

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

- a. General epidemiological surveillance

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

- b. Specific surveillance

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

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

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

- a. prescribed by a veterinarian or other authorised person;
- b. supplied only through licensed/authorised distribution systems;
- c. administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons;

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

13. Control of advertising

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

- a. complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics;
- b. is restricted to authorised professionals, according to national legislation in each country.

14. Training of antimicrobial users

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

- a. information on disease prevention and management strategies;
- b. the ability of antimicrobials to select for resistance in food-producing animals;
- c. the need to observe responsible use recommendations for the use of *antimicrobial agents* in animal husbandry in agreement with the provisions of the marketing authorisations.

15. Research

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

Article 3.9.3.4.

Responsibilities of the veterinary pharmaceutical industry

1. Marketing authorisation of VAPs

The veterinary pharmaceutical industry has responsibilities to:

- a. supply all the information requested by the national regulatory authorities;
- b. guarantee the quality of this information in compliance with the provisions of good manufacturing, laboratory and clinical practices;
- c. implement a pharmacovigilance programme and on request, specific surveillance for bacterial susceptibility and resistance.

2. Marketing and export of VAPs

For the marketing and export of VAPs:

- a. only licensed and officially approved VAPs should be sold and supplied, and then only through licensed/authorised distribution systems;
- b. the pharmaceutical industry should provide quality certificates prepared by the Competent Authority of the exporting and/or manufacturing countries to the importing country;
- c. the national regulatory authority should be provided with the information necessary to evaluate the amount of antimicrobial agents marketed.

3. Advertising

The veterinary pharmaceutical industry should:

- a. disseminate information in compliance with the provisions of the granted authorisation;
- b. ensure that the advertising of antimicrobials directly to the food animal producer is discouraged.

4. Training

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

5. Research

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

Article 3.9.3.5.

Responsibilities of wholesale and retail distributors

1. Retailers distributing VAPs should only do so on the prescription of a veterinarian or other suitably trained person authorised in accordance with national legislation, and all products should be appropriately labelled.
2. The guidelines on the responsible use of antimicrobials should be reinforced by retail distributors who should keep detailed records of:
 - a. date of supply;
 - b. name of prescriber;
 - c. name of user;
 - d. name of product;
 - e. batch number;
 - f. quantity supplied.
3. Distributors should also be involved in training programmes on the responsible use of antimicrobials, as defined in point 14 of Article 3.9.3.3.

Article 3.9.3.6.

Responsibilities of veterinarians

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

Veterinarians should only prescribe antimicrobials for animals under their care.

1. Use of antimicrobial agents

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

- a. only prescribe antimicrobials when necessary;
- b. make an appropriate choice of the antimicrobial based on experience of the efficacy of treatment.

2. Choosing an antimicrobial agent

- a. The expected efficacy of the treatment is based on:
 - i. the clinical experience of the veterinarian;
 - ii. the activity towards the pathogens involved;
 - iii. the appropriate route of administration;
 - iv. known pharmacokinetics/tissue distribution to ensure that the selected therapeutic agent is active at the site of infection;
 - v. the epidemiological history of the rearing unit, particularly in relation to the antimicrobial resistance profiles of the pathogens involved.

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

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

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

- b. Use of combinations of antimicrobials should be scientifically supported. Combinations of antimicrobials may be used for their synergistic effect to increase therapeutic efficacy or to broaden the spectrum of activity.

3. Appropriate use of the antimicrobial chosen

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

The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the withdrawal periods to be used. It is the veterinarian's responsibility to define the conditions of responsible use in such a case including the therapeutic regimen, the route of administration, and the duration of the treatment.

4. Recording

Records on veterinary antimicrobial drugs should be kept in conformity with national legislation. Information records should include the following:

- a. quantities of medication used;
- b. a list of all medicines supplied to each food-producing animal holding;
- c. a list of medicine withdrawal period;
- d. a record of antimicrobial susceptibilities;
- e. comments concerning the response of animals to medication;
- f. the investigation of adverse reactions to antimicrobial treatment, including lack of response due to antimicrobial resistance. Suspected adverse reactions should be reported to the appropriate regulatory authorities.

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

5. Labelling

All medicines supplied by a veterinarian should be labelled according to national legislation.

6. Training

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

Article 3.9.3.7.

Responsibilities of food-animal producers

1. Food-animal producers with the assistance of a veterinarian are responsible for implementing health and welfare programmes on their farms (good farming practice) in order to promote animal health and food safety.
2. Food-animal producers should:
 - a. draw up a health plan with the attending veterinarian that outlines preventative measures (feedlot health plans, mastitis control plans, endo- and ectoparasite control and vaccination programmes, etc.);
 - b. use antimicrobial agents only on prescription, and according to the provisions of the prescription;
 - c. use antimicrobial agents in the species, for the uses and at the dosages on the approved/registered labels and in accordance with product label instructions or the advice of a veterinarian familiar with the animals and the production site;
 - d. isolate sick animals, when appropriate, to avoid the transfer of pathogens; dispose of dead or dying animals promptly under conditions approved by the relevant authorities;
 - e. comply with the storage conditions of antimicrobials in the rearing unit, according to the provisions of the leaflet and package insert;
 - f. address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated;
 - g. comply with the recommended withdrawal periods to ensure that residue levels in animal-derived food do not present a risk for the consumer;
 - h. dispose of surplus antimicrobials under safe conditions for the environment; medicines should only be used within the expiry date, for the condition for which they were prescribed and, if possible, in consultation with the prescribing veterinarian;
 - i. maintain all the laboratory records of bacteriological and susceptibility tests; these data should be made available to the veterinarian responsible for treating the animals;
 - j. keep adequate records of all medicines used, including the following:
 - i. name of the product/active substance and batch number;
 - ii. name of prescriber and/or the supplier;
 - iii. date of administration;
 - iv. identification of the animal or group of animals to which the antimicrobial agent was administered;
 - v. clinical conditions treated;
 - vi. dosage;
 - vii. withdrawal periods;

- viii. result of laboratory tests;
- ix. effectiveness of therapy;
- k. inform the responsible veterinarian of recurrent disease problems.

CODEX CODE OF PRACTICE TO MINIMISE AND CONTAIN ANTIMICROBIAL RESISTANCE

CAC/RCP 61-2005

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INTRODUCTION

1. This document provides additional guidance for the responsible and prudent use of antimicrobials in food-producing animals, and should be read in conjunction with the Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993. Its objectives are to minimize the potential adverse impact on public health resulting from the use of antimicrobial agents in food-producing animals, in particular the development of antimicrobial resistance. It is also important to provide for the safe and effective use of veterinary antimicrobial drugs in veterinary medicine by maintaining their efficacy. This document defines the respective responsibilities of authorities and groups involved in the authorization, production, control, distribution and use of veterinary antimicrobials such as the national regulatory authorities, the veterinary pharmaceutical industry, veterinarians, distributors and producers of food-producing animals.
2. The marketing authorization procedure has a significant role in establishing the basis for prudent use of veterinary antimicrobial drugs in food-producing animals through clear label indications, directions and warning statements.
3. A number of codes of practice relating to the use of veterinary antimicrobial drugs and the conditions thereof have been developed by different organisations. These codes were taken into consideration and some elements were included in the elaboration of this Code of Practice to Minimize and Contain Antimicrobial Resistance.
4. In keeping with the Codex mission, this Code focuses on antimicrobial use in food-producing animals. It is recognized that antimicrobial resistance is also an ecological problem and that management of antimicrobial resistance may require addressing the persistence of resistant microorganisms in the environment. Although this issue is most relevant for CCRVDF with respect to food-producing animals, the same principles apply to companion animals, which also harbor resistant microorganisms.

AIMS AND OBJECTIVES

5. It is imperative that all who are involved in the authorisation, manufacture, sale and supply, prescription and use of antimicrobials in food-producing animals act legally, responsibly and with the utmost care in order to limit the spread of resistant microorganisms among animals so as to protect the health of consumers.
6. Antimicrobial drugs are powerful tools for the management of infectious diseases in animals and humans. This Code and existing guidelines for the responsible use of antimicrobial drugs in food-producing animals include recommendations intended to prevent or reduce the selection of antimicrobial resistant microorganisms in animals and humans in order to:
 - Protect consumer health by ensuring the safety of food of animal origin intended for human consumption.
 - Prevent or reduce as far as possible the direct and indirect transfer of resistant microorganisms or resistance determinants within animal populations and from food-producing animals to humans.
 - Prevent the contamination of animal derived food with antimicrobial residues which exceed the established MRL.
 - Comply with the ethical obligation and economic need to maintain animal health.

7. This Code does not address environmental issues related to antimicrobial resistance from the use of veterinary antimicrobial drugs but it encourages all those involved to consider the ecological aspects when implementing the Code. Efforts should be made to ensure that environmental reservoirs of veterinary antimicrobial drugs, antimicrobial resistant organisms and resistance determinants are kept to a minimum. In particular:

- Regulatory authorities should assess the impact of proposed veterinary antimicrobial drug use on the environment in accordance with national guidelines or recognized international guidelines⁵
- Research should be conducted on resistant microorganisms in the environment and the magnitude of resistance determinant transfer among microorganisms in the environment.

8. The responsible use of veterinary antimicrobial drugs in food-producing animals:

- is controlled by the veterinary profession or other parties with the required expertise.
- is part of good veterinary and good animal husbandry practice and takes into consideration disease prevention practices such as the use of vaccination and improvements in husbandry conditions.
- aims to limit the use of veterinary antimicrobial drugs according to their approved and intended uses, and takes into consideration on-farm sampling and testing of isolates from food-producing animals during their production, where appropriate, and makes adjustments to treatment when problems become evident.
- should be based on the results of resistance surveillance and monitoring (microbial cultures and antimicrobial sensitivity testing), as well as clinical experience.
- does not include the use for growth promotion of veterinary antimicrobial drugs that belong to or are able to cause cross resistance to classes of antimicrobial agents used (or submitted for approval) in humans in the absence of a risk analysis. This risk analysis should:
 - be undertaken by the appropriate national regulatory authority;
 - be based on adequate scientific evidence; and
 - focus on the potential to impact resistance to antimicrobials used in human medicine.
- is aimed at all the relevant parties, such as:
 - regulatory and scientific authorities;
 - the veterinary pharmaceutical industry;
 - distributors and others handling veterinary antimicrobial drugs;
 - veterinarians, pharmacists and producers of food-producing animals.

⁵ VICH (2000). Guidelines on Environmental Impact Assessment for Veterinary Medicinal Products, Phase I. http://vich.eudra.org/pdf/2000/G106_st7.pdf

RESPONSIBILITIES OF THE REGULATORY AUTHORITIES

9. The national regulatory authorities, which are responsible for granting the marketing authorisation for antimicrobials for use in food-producing animals, have a significant role in specifying the terms of this authorisation and in providing the appropriate information to the veterinarian through product labelling and/or by other means, in support of prudent use of veterinary antimicrobial drugs in food-producing animals. It is the responsibility of regulatory authorities to develop up-to-date guidelines on data requirements for evaluation of veterinary antimicrobial drug applications. National governments in cooperation with animal and public health professionals should adopt a proactive approach to promote prudent use of antimicrobials in food-producing animals as an element of a national strategy for the containment of antimicrobial resistance. Other elements of the national strategy should include good animal husbandry practices, vaccination policies and development of animal health care at the farm level, all of which should contribute to reduce the prevalence of animal disease requiring antimicrobial treatment. Use of veterinary antimicrobial drugs for growth promotion that belong to classes of antimicrobial agents used (or submitted for approval) in humans and animals should be terminated or phased out in the absence of risk-analysis, as described in Paragraph 8.

10. It is the responsibility of the pharmaceutical company or sponsor⁶ to submit the data requested by the regulatory authorities for granting marketing authorisation.

11. The use of antimicrobial agents in food-producing animals requires a marketing authorisation, granted by the competent authorities when the criteria of safety, quality and efficacy are met.

- The examination of dossiers/drug applications should include an assessment of the risks to both animals and humans resulting from the use of antimicrobial agents in food-producing animals. The evaluation should focus on each individual veterinary antimicrobial drug but take into consideration the class of antimicrobials to which the particular active principle belongs.
- The safety evaluation should include consideration of the potential impact of the proposed use in food-producing animals on human health, including the human health impact of antimicrobial resistance developing in microorganisms found in food-producing animals and their environment associated with the use of veterinary antimicrobial drugs.

12. If dose ranges or different durations of treatment are indicated, the national authorities should give guidance on the approved product labelling regarding the conditions that will minimize the development of resistance, when this information is available.

13. The relevant authorities should make sure that all the antimicrobial agents used in food-producing animals are prescribed by a veterinarian or other suitably trained person authorized in accordance with national legislation or used under conditions stipulated in the national legislation. (See OIE Guidelines for Antimicrobial Resistance: Responsible and Prudent Use of Antimicrobial Agents in Veterinary Medicine (Terrestrial Animal Health Code, Appendix 3.9.3)

14. No veterinary antimicrobial drug should be administered to animals unless it has been evaluated and authorized for such use by the relevant authorities or the use is allowed through off-label guidance or legislation. Regulatory authorities should, where possible, expedite the market approval process of new veterinary antimicrobial drug formulations considered to have the potential to make an important contribution in the control of antimicrobial resistance.

⁶ As defined in the VICH Good Clinical Practice Guideline, http://vich.eudra.org/pdf/2000/GI09_st7.pdf

15. Countries without the necessary resources to implement an efficient authorisation procedure for veterinary antimicrobial drugs and whose supply of veterinary antimicrobial drugs mostly depends on imports from foreign countries should:

- ensure the efficacy of their administrative controls on the import of these veterinary antimicrobial drugs,
- seek information on authorizations valid in other countries, and
- develop the necessary technical cooperation with experienced authorities to check the quality of imported veterinary antimicrobial drugs as well as the validity of the recommended conditions of use. Alternatively, a national authority could delegate a competent institution to provide quality certification of veterinary antimicrobial drugs.

16. All countries should make every effort to actively combat the manufacture, advertisement, trade, distribution and use of illegal and/or counterfeit bulk active pharmaceutical ingredients and products. Regulatory authorities of importing countries could request the pharmaceutical industry to provide quality certificates or, where feasible, certificates of Good Manufacturing Practices prepared by the exporting country's national regulatory authority.

Quality Control of Antimicrobial Agents

17. Regulatory authorities should ensure that quality controls are carried out in accordance with international guidance and in compliance with the provisions of good manufacturing practices, in particular:

- to ensure that the quality and concentration (stability) of veterinary antimicrobial drugs in the marketed dosage form(s) is maintained and properly stored up to the expiry date, established under the recommended storage conditions.
- to ensure the stability of veterinary antimicrobial drugs when they are mixed with feed or drinking water.
- to ensure that all veterinary antimicrobial drugs are manufactured to the appropriate quality and purity.

Assessment of Efficacy

18. Preclinical data should be generated to establish an appropriate dosage regimen necessary to ensure the efficacy of the veterinary antimicrobial drug and limit the selection of microbial resistant microorganisms. Such preclinical trials should, where applicable, include pharmacokinetic and pharmacodynamic studies to guide the development of the most appropriate dosage regimen.

19. Important pharmacodynamic information may include:

- mode of action;
- the spectrum of antimicrobial activity of the substance;
- identification of bacterial species that are naturally resistant relevant to the use of the veterinary antimicrobial drugs;
- antimicrobial minimum inhibitory and/or bactericidal concentrations;

- determination of whether the antimicrobial exhibits time or concentration-dependent activity or co-dependency,
 - evaluation of activity at the site of infection.
20. Important pharmacokinetic information may include:
- bio-availability according to the route of administration;
 - concentration of the veterinary antimicrobial drug at the site of infection and its distribution in the treated animal;
 - metabolism which may lead to the inactivation of veterinary antimicrobial drugs;
 - excretion routes.
21. The use of fixed combinations of veterinary antimicrobial drugs should be justified taking into account:
- pharmacodynamic (additive or synergistic effects towards the target microorganism);
 - pharmacokinetics (maintenance of the concentrations of associated antimicrobials responsible for additive or synergistic effects at the site of infection throughout the treatment period).
22. Clinical data should be generated to confirm the validity of the claimed indications and dosage regimens established during the preclinical phase.
23. Criteria to be considered include:
- parameters for qualitatively and quantitatively assessing efficacy;
 - diversity of the clinical cases met when carrying out clinical trials;
 - compliance of the protocols of clinical trials with good clinical practice, such as VICH guidelines⁷;
 - eligibility of the studied clinical cases based on appropriate clinical and microbiological criteria.

Assessment of the potential of veterinary antimicrobial drugs to select for resistant microorganisms

24. Where applicable, data from preclinical or clinical trials should be used to evaluate the potential for target microorganisms, foodborne and/or commensal microorganisms to develop or acquire resistance.

25. Appropriate information should be provided to support an adequate assessment of the safety of veterinary antimicrobial drugs being considered for authorisation in food-producing animals. The regulatory authorities should develop criteria for conducting such assessments and interpreting their results. Existing guidelines for antimicrobial resistance risk assessment, such as the OIE Guideline⁸ may be used for more comprehensive information. The type of information to be evaluated in these assessments may include, but is not limited to, the following:

⁷ VICH Good Clinical Practice Guideline , http://vich.eudra.org/pdf/2000/G109_st7.pdf

⁸ Antimicrobial resistance: risk analysis methodology for the potential impact on public health of antimicrobial resistant bacteria of animal origin, http://www.oie.int/eng/publicat/rt/2003a_r20314.htm

- the route and level of human exposure to food-borne or other resistant microorganisms;
- the degree of cross resistance within the class of antimicrobials and between classes of antimicrobials;
- the pre-existing level of resistance, if available, in pathogens causing gastrointestinal infections in humans (baseline determination);
- the concentration of active compound in the gut of the animal at the defined dosage level.

Establishment of ADIs (acceptable daily intake), MRLs (maximum residue limit), and withdrawal periods for veterinary antimicrobial drugs

26. When setting ADIs and MRLs for veterinary antimicrobial drugs, the safety evaluation is carried out in accordance with international guidelines and should include the determination of microbiological effects (e.g., the potential biological effects on the human intestinal flora) as well as toxicological and pharmacological effects.

27. An acceptable daily intake (ADI) and a maximum residue limit (MRL) for appropriate food stuffs (i.e., meat, milk, eggs, fish and honey) should be established for each antimicrobial agent. MRLs are necessary in order that officially recognised control laboratories can monitor that the veterinary antimicrobial drugs are being used as approved. Withdrawal periods should be established for each veterinary antimicrobial drug, which make it possible to produce food in compliance with the MRLs.

28. Withdrawal periods have to be established for each veterinary antimicrobial drug by taking into account:

- the MRLs established for the considered veterinary antimicrobial drug;
- the pharmaceutical form;
- the target animal species;
- the dosage regimen and the duration of treatment;
- the route of administration.

Establishment of a summary of product characteristics for each veterinary antimicrobial drug for food-producing animals

29. The summary of product characteristics contains the information necessary for the appropriate use of veterinary antimicrobial drugs. It constitutes, for each veterinary antimicrobial drug, the official reference of the content of its labelling and package insert. This summary contains the following items:

- pharmacological properties;
- target animal species;
- indications;
- target microorganisms;
- dosage and administration route;
- withdrawal periods;

- incompatibilities;
- shelf-life;
- operator safety;
- particular precautions before use;
- instructions for the return or proper disposal of un-used or out-of-date products;
- any information on conditions of use relevant to the potential for selection of resistance should be included, for the purpose of guidance on prudent use;
- class and active ingredient of the veterinary antimicrobial drug.

Surveillance Programmes

30. The relevant authorities should develop a structured approach to the investigation and reporting of the incidence and prevalence of antimicrobial resistance. For the purposes of this Code, priority should be given to the evaluation of antimicrobial resistance in foodborne microorganisms.

For reasons of efficiency, the methods used to establish such programmes (laboratory techniques, sampling, choice of veterinary antimicrobial drug(s) and microorganism(s)) should be harmonized as much as possible at the international level (e.g. OIE documents on “Harmonisation of National Antimicrobial Resistance Monitoring and Surveillance Programmes in Animals and Animal Derived Food” http://www.oie.int/eng/publicat/rt/2003/a_r20318.htm and “Standardisation and Harmonisation of Laboratory Methodologies Used for the Detection and Quantification of Antimicrobial Resistance” http://www.oie.int/eng/publicat/rt/2003/a_r20317.htm).

31. Preferably, epidemiological surveillance of antimicrobial resistance should be accompanied by data on the amounts of veterinary antimicrobial drugs used by veterinarians and other authorized users in food-producing animals. These data could be collected using one or more of the following sources:

- production data from manufacturers;
- importers and exporters;
- if possible, data on intended and actual usage from manufacturers, wholesale and retail distributors including feed mills, and veterinary prescription records;
- surveys of veterinarians, farmers and producers of food-producing animals.

32. Regulatory authorities should have in place a pharmacovigilance programme for the monitoring and reporting of adverse reactions to veterinary antimicrobial drugs, including lack of the expected efficacy related to microbial resistance. The information collected through the pharmacovigilance programme should form part of the comprehensive strategy to minimize microbial resistance.

33. In cases, where the assessment of data collected from pharmacovigilance and from other post-authorization surveillance including, if available, targeted surveillance of antimicrobial resistance, suggests that the conditions of use of the given veterinary antimicrobial drug should be reviewed, regulatory authorities shall endeavour to achieve this re-evaluation.

Distribution of veterinary antimicrobial drugs in veterinary medicine

34. The relevant authorities should make sure that all veterinary antimicrobial drugs used in food-producing animals are, to the extent possible:

- prescribed by a veterinarian or other suitably trained person authorized in accordance with national legislation or used under conditions stipulated in the national legislation;
- supplied only through licensed/authorized distribution systems;
- administered to animals by a veterinarian or, under the supervision of a veterinarian or other suitably trained person authorized in accordance with national legislation; and that
- proper records are kept of their administration (see Paragraph 58, Responsibilities of Veterinarians: Recording section).

Control of advertising

35. Advertising of veterinary antimicrobial drugs should be done in a manner consistent with prudent use guidelines and any other specific regulatory recommendation for the product.

All advertising of veterinary antimicrobial drugs should be controlled by the relevant authorities.

- The authorities should ensure that advertising of veterinary antimicrobial drugs:
 - complies with the marketing authorisation granted, in particular with the content of the summary of product characteristics; and
 - complies with each country's national legislation.

Training of users of veterinary antimicrobial drugs

36. Training should be undertaken to assure the safety to the consumer of animal derived food and therefore the protection of public health. Training should involve all the relevant professional organisations, regulatory authorities, the pharmaceutical industry, veterinary schools, research institutes, professional associations and other approved users such as farmers and producers of food animals and should focus on:

- information on disease prevention and management strategies to reduce the need to use veterinary antimicrobial drugs;
- relevant pharmacokinetic and pharmacodynamic information to enable the veterinarian to use veterinary antimicrobial drugs prudently;
- the ability of veterinary antimicrobial drugs to select for resistant microorganisms in food-producing animals that may contribute to animal or human health problems; and
- the need to observe responsible use recommendations and using veterinary antimicrobial drugs in animal husbandry in agreement with the provisions of the marketing authorisations and veterinary advice.

Development of research

37. The relevant authorities should encourage public and private research to:
- improve the knowledge about the mechanisms of action of antimicrobials in order to optimise the dosage regimens and their efficacy;
 - improve the knowledge about the mechanisms of selection, emergence and dissemination of resistance determinants;
 - develop practical models for applying the concept of risk analysis to assess the public health concern precipitated by the development of resistance;
 - further develop protocols to predict, during the authorisation process, the impact of the proposed use of the veterinary antimicrobial drugs on the rate and extent of resistance development; and
 - develop and encourage alternative methods to prevent infectious diseases.

Collection and destruction of unused veterinary antimicrobial drugs

38. The relevant authorities should develop effective procedures for the safe collection and destruction of unused or out-of-date veterinary antimicrobial drugs.

RESPONSIBILITIES OF THE VETERINARY PHARMACEUTICAL INDUSTRY

Marketing authorisation of veterinary antimicrobial drugs for food-producing animals

39. It is the responsibility of the veterinary pharmaceutical industry:
- to supply all of the information requested by the national regulatory authority in order to establish objectively the quality, safety and efficacy of veterinary antimicrobial drugs; and
 - to ensure the quality of this information on the basis of the implementation of procedures, tests and trials in compliance with the provisions of good manufacturing, good laboratory and good clinical practices.

Marketing and export of veterinary antimicrobial drugs

40. Only officially licensed/authorized veterinary antimicrobial drugs should be marketed, and then only through approved distribution systems.
- Only veterinary antimicrobial drugs meeting the quality standards of the importing country should be exported from a country in which the products were produced;
 - The information necessary to evaluate the amount of veterinary antimicrobial drugs marketed should be provided to the national regulatory authority.

Advertising

41. It is the responsibility of the veterinary pharmaceutical industry to advertise veterinary antimicrobial drugs in accordance with the provisions of Paragraph 35 on the Responsibilities of the Regulatory Authorities, Control of Advertising and to not inappropriately advertise antimicrobials directly to the food animal producer.

Training

42. It is the responsibility of the veterinary pharmaceutical industry to participate in the training of users of veterinary antimicrobial drugs as defined in Paragraph 36.

Research

43. It is the responsibility of the veterinary pharmaceutical industry to contribute to the development of research as defined in Paragraph 37.

RESPONSIBILITIES OF WHOLESALE AND RETAIL DISTRIBUTORS

44. Retailers distributing veterinary antimicrobial drugs should only do so on the prescription of a veterinarian or other suitably trained person authorized in accordance with national legislation and all products should be appropriately labelled.

45. Distributors should encourage compliance with the national guidelines on the responsible use of veterinary antimicrobial drugs and should keep detailed records of all antimicrobials supplied according to the national regulations including:

- date of supply
- name of prescribing veterinarian
- name of user
- name of medicinal product
- batch number
- quantity supplied

46. Distributors should participate in the training of users of veterinary antimicrobial drugs as defined in Paragraph 36.

RESPONSIBILITIES OF VETERINARIANS⁹

47. The veterinarian is responsible for identifying recurrent disease problems and developing alternative strategies to prevent or treat infectious disease. These may include changes in husbandry conditions and vaccination programs where vaccines are available.

48. Veterinary antimicrobial drugs should only be prescribed for animals under his/her care, which means that:

⁹ Under some circumstances, this may refer to a suitably trained person authorized in accordance with national legislation.

- the veterinarian has been given responsibility for the health of the animal or herd/flock by the producer or the producer's agent;
- that responsibility is real and not merely nominal;
- that the animal(s) or herd/flock have been seen immediately before the prescription and supply, or
- recently enough for the veterinarian to have personal knowledge of the condition of the animal(s) or current health status of the herd or flock to make a diagnosis and prescribe; and
- the veterinarian should maintain clinical records of the animal(s) or the herd/flock.

49. It is recommended that veterinary professional organizations develop for their members species-specific clinical practice guidelines on the responsible use of veterinary antimicrobial drugs.

50. Veterinary antimicrobial drugs should only be used when necessary and in an appropriate manner:

- A prescription for veterinary antimicrobial drugs must precisely indicate the treatment regimen, the dose, the dosage intervals, the duration of the treatment, the withdrawal period and the amount of antimicrobial to be delivered depending on the dosage, the number, and the weight of the animals to be treated;
- All veterinary antimicrobial drugs should be prescribed and used according to the conditions stipulated in the national legislation.

51. The appropriate use of veterinary antimicrobial drugs in practice is a clinical decision which should be based on the experience and local expertise of the prescribing veterinarian, and the accurate diagnosis, based on adequate diagnostic procedures. There will be occasions when a group of animals, which may have been exposed to pathogens, may need to be treated without recourse to an accurate diagnosis and antimicrobial susceptibility testing in order to prevent the development of clinical disease and for reasons of animal welfare.

52. Determination of the choice of a veterinary antimicrobial drug by:

- The expected efficacy of the treatment based on:
 - the clinical experience of the veterinarian;
 - the spectrum of the antimicrobial activity towards the pathogens involved;
 - the epidemiological history of the rearing unit particularly in regards to the antimicrobial resistance profiles of the pathogens involved. Ideally, the antimicrobial profiles should be established before the commencement of treatment. Should a first antimicrobial treatment fail or should the disease recur, the use of a second veterinary antimicrobial drug should be based on the results of microbiological tests;
 - the appropriate route of administration;
 - results of initial treatment;
 - known pharmacokinetics/tissue distribution to ensure that the selected veterinary antimicrobial drug is active at the site of infection;
 - prognosis.

- The need to minimize the adverse health impact from the development of microbial resistance based on:
 - the choice of the activity spectrum of the veterinary antimicrobial drug;
 - the targeting of specific microorganism;
 - known or predictable susceptibilities using antimicrobial susceptibility testing;
 - optimized dosing regimens;
 - the use of effective combinations of veterinary antimicrobial drugs;
 - the importance of the antimicrobial drugs to veterinary and human medicine; and,
 - the route of administration.

53. If the label conditions allow for some flexibility, the veterinarian should consider a dosage regimen that is long enough to allow an effective recovery of the animal but is short enough to limit the selection of resistance in foodborne and/or commensal microorganisms.

Off-label use

54. The off-label use of a veterinary antimicrobial drug may be permitted in appropriate circumstances and should be in agreement with the national legislation in force including the administrative withdrawal periods to be used. It is the veterinarian's responsibility to define the conditions of responsible use in such a case including the therapeutic regimen, the route of administration, and the duration of the treatment. Off-label use of antimicrobial growth promoters should not be permitted.

Recording

55. Records on veterinary antimicrobial drugs should be kept in conformity with national legislation. Veterinarians may refer to recording information as covered in the relevant national legislation.¹⁰

In particular, for investigation of antimicrobial resistance, veterinarians should:

- record the antimicrobial susceptibility testing results;
- investigate adverse reactions to veterinary antimicrobial drugs, including lack of expected efficacy due to antimicrobial resistance, and report it, as appropriate, to the regulatory authorities.

56. Veterinarians should also periodically review farm records on the use of veterinary antimicrobial drugs to ensure compliance with their directions.

Training

57. Veterinary professional organizations should participate in the training of users of veterinary antimicrobial drugs as defined in Paragraph 36.

¹⁰ Veterinarians can also refer to the "Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993."

RESPONSIBILITIES OF PRODUCERS

58. Producers are responsible for preventing disease outbreaks and implementing health and welfare programmes on their farms. They may, as appropriate, call on the assistance of their veterinarian or other suitably trained person authorized in accordance with national legislation. All people involved with food-producing animals have an important part to play in ensuring the responsible use of veterinary antimicrobial drugs.

59. Producers of food-producing animals have the following responsibilities:

- to use veterinary antimicrobial drugs only when necessary and not as a replacement for good management and farm hygiene, or other disease prevention methods such as vaccination;
- to implement a health plan in cooperation with the veterinarian in charge of the animals that outlines preventative measures (e.g. mastitis plan, worming and vaccination programmes, etc.);
- to use veterinary antimicrobial drugs in the species, for the uses and at the doses on the approved labels and in accordance with the prescription, product label instructions or the advice of a veterinarian familiar with the animals and the production site;
- to isolate sick animals and dispose of dead or dying animals promptly under conditions approved by relevant authorities;
- to comply with the storage conditions of veterinary antimicrobial drugs according to the approved product labelling;
- to address hygienic conditions regarding contacts between people (veterinarians, breeders, owners, children) and the animals treated;
- to comply with the recommended withdrawal periods to ensure that residue levels in animal derived food do not present a risk for the consumer;
- to not use out-of-date veterinary antimicrobial drugs and to dispose of all unused veterinary antimicrobial drugs in accordance with the provisions on the product labels;
- to inform the veterinarian in charge of the unit of recurrent disease problems;
- to maintain all clinical and laboratory records of microbiological and susceptibility tests if required by the national regulatory authority. These data should be made available to the veterinarian in charge of treating the animals in order to optimize the use of veterinary antimicrobial drugs.
- To keep adequate records of all veterinary antimicrobial drugs used, including the following:
 - name of the veterinary antimicrobial drug/active substance and batch number;
 - name of supplier;
 - date of administration;
 - identification of the animal or group of animals to which the veterinary antimicrobial drug was administered;
 - clinical conditions treated;
 - quantity and duration of the antimicrobial agent administered;

- withdrawal periods;
 - result of laboratory tests;
 - result of treatment;
 - name of the prescribing veterinarian or other suitably trained person authorized in accordance with national legislation.
- To ensure sound management of animal wastes and other materials to avoid dissemination of antimicrobial agents and resistance determinants into the environment;
 - To prevent the unnecessary contact with and transmission of resistant bacteria to all personnel, including farm workers;
 - To assist the relevant authorities in surveillance programs related to antimicrobial resistance.

CONCLUSIONS

60. Veterinary antimicrobial drugs are very important tools for controlling a great number of infectious diseases in both animals and humans. It is vital that all countries put in place the appropriate systems to ensure that veterinary antimicrobial drugs are manufactured, marketed, distributed, prescribed and used responsibly, and that these systems are adequately audited.

61. This document is designed to provide the framework that countries may implement in accordance with their capabilities but within a reasonable period of time. A stepwise approach may be appropriate for a number of countries to properly implement all of the elements in this document.

62. The continued availability of veterinary antimicrobial drugs, which are essential for animal welfare and animal health and consequently human health, will ultimately depend on the responsible use of these products by all those involved in the authorisation, production, control, distribution and use of antimicrobials in food-producing animals.

ENDNOTES:

¹A. Franklin, J. Acar, F. Anthony, R. Gupta †T. Nicholls, Y. Tamura, S. Thompson, E.J. Threlfall, D. Vose, M. van Vuuren, D.G. White, H. C. Wegener & M.L. Costarrica. *Antimicrobial resistance: harmonization of national antimicrobial resistance monitoring and surveillance programmes in animals and in animal-derived food*. *Rev. sci. tech. Off. Int. Epiz.*, **20** (3), 859-870. http://www.oie.int/eng/publicat/rt/2003/a_r20318.htm

²D.G. White, J. Acar, F. Anthony, A. Franklin, R. Gupta, †T. Nicholls, Y. Tamura, S. Thompson, E.J. Threlfall, D. Vose, M. van Vuuren, H. C. Wegener & M.L. Costarrica. *Antimicrobial resistance: standardization and harmonization of laboratory methodologies for the detection and quantification of antimicrobial resistance*. *Rev. sci. tech. Off. Int. Epiz.*, 2001, **20** (3), 849-858. http://www.oie.int/eng/publicat/rt/2003/a_r20317.htm

LIST OF ABBREVIATIONS USED IN THIS CODE

ADI	Acceptable Daily Intake
CAC	Codex Alimentarius Commission
CAC/RCP	Codex Alimentarius Commission/Recommended Code of Practice
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
FAO	Food and Agriculture Organization of the United Nations
MRL	Maximum Residue Limit
OIE	World Organisation for Animal Health
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organization

GLOSSARY AND DEFINITION OF TERMS

Veterinary Antimicrobial Drug

Veterinary antimicrobial drug(s) refers to naturally occurring, semi-synthetic or synthetic substances that exhibit antimicrobial activity (kill or inhibit the growth of microorganisms). Where anticoccidial products have antibacterial activity, they should be considered as veterinary antimicrobial drugs, except where this is precluded by national legislation.

Disease Treatment/Therapeutic Use

Treatment/Therapeutic Use refers to use of an antimicrobial(s) for the specific purpose of treating an animal(s) with a clinically diagnosed infectious disease or illness.

Disease Prevention/Prophylactic Use

Prevention/Prophylactic Use refers to use of an antimicrobial(s) in healthy animals considered to be at risk of infection or prior to the onset of clinical infectious disease. This treatment includes:

- control of the dissemination of a clinically diagnosed infectious disease identified within a group of animals, and
- prevention of an infectious disease that has not yet been clinically diagnosed.

Growth Promotion

Growth Promotion refers to the use of antimicrobial substances to increase the rate of weight gain and/or the efficiency of feed utilization in animals by other than purely nutritional means. The term does NOT apply to the use of antimicrobials for the specific purpose of treating, controlling, or preventing infectious diseases, even when an incidental growth response may be obtained.

THE CODEX CODE OF PRACTICE FOR FISH AND FISHERY PRODUCTS
(CAC/RCP 52-2003, Rev. 2-2005. Sections relevant to Aquaculture)

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INTRODUCTION

This Code of Practice for Fish and Fishery Products has been developed by the Codex Committee on Fish and Fishery Products from the merging of the individual codes listed in Appendix XII* plus a section on aquaculture and a section on frozen surimi. These codes were primarily of a technological nature offering general advice on the production, storage and handling of fish fishery products on board fishing vessels and on shore. It also deals with the distribution and retail display of fish and fishery products.

This combined Code of practice has been further modified to incorporate the Hazard Analysis Critical Control Point (HACCP) approach described in the *Recommended International Code of Practice – General Principles of Food Hygiene* (CAC/RCP 1-1969, Rev.3 1997), Annex: *HACCP System and Guidelines for its Application*. A pre-requisite programme is described in the Code covering technological guidelines and the essential requirements of hygiene in the production of fish, shellfish and their products, which are safe for human consumption, and otherwise meets the requirements of the appropriate Codex product standards. The Code also contains guidance on the use of HACCP, which is recommended to ensure the hygienic production of fish and fishery products to meet health and safety requirements.

Within this Code a similar systematic approach has been applied to essential quality, composition and labelling provisions of the appropriate Codex product standards. Throughout the code this is referred to as “Defect Action Point (DAP) Analysis”. However DAP analysis is optional.

The Codex Committee on Fish and Fishery Products recommended at its Twentieth Session that defects of a commercial nature, i.e. workmanship defects, which had been removed from Codex fish product standards, be transferred to the appropriate Codex Code of practice for optional use between buyers and sellers during commercial transactions. The Committee further recommended that this detail should be described in a section on Final Product Specifications, which now appear as Appendices II - XI* of this document. A similar approach to HACCP has been incorporated into the Code as guidelines for the control of defects (DAP Analysis).

This Code will assist all those who are engaged in the handling and production of fish and fishery products, or are concerned with their storage, distribution, export, import and sale in attaining safe and wholesome products which can be sold on national or international markets and meet the requirements of the Codex Standards (see Appendix XII*).

HOW TO USE THIS CODE

The aim of this Code is to provide a user-friendly document as background information and guidance for the elaboration of fish and shellfish process management systems which would incorporate Good Management Practice (GMP) as well as the application of HACCP in countries where these, as yet, have not been developed. In addition, it could be used for training of fishermen and employees of the fish and shellfish processing industries.

* Under development

The practical application of this *international* Code, with regard to *national* fisheries, would therefore require some modifications and amendments, taking into account local conditions and specific consumer requirements. This Code, therefore, is not intended to replace the advice or guidance of trained and experienced technologists regarding the complex technological and hygienic problems which might be unique to a specific geographical area or specific fishery and, in fact, is intended to be used as a supplement in such instances.

This Code is divided into separate, though interrelated, Sections. It is intended that in order to set up a HACCP or DAP programme these should be consulted as appropriate:

- (a) *Section 2 - Definitions* – Being acquainted with the definitions is important and will aid the overall understanding of the Code.
- (b) *Section 3 - Pre-requisite Programme* - Before HACCP or a similar approach can properly be applied to a process it is important that a solid foundation of good hygienic practice exists. This Section covers the groundwork which should be regarded as the minimum requirements for a facility prior to the application of hazard and defect analyses.
- (c) *Section 4 – General Considerations for the Handling of Fresh Fish, Shellfish and Other Aquatic Invertebrates* – This Section provides an overall view of the potential hazards and defects which may have to be considered when building up a HACCP or DAP plan. This is not intended to be an exhaustive list but is designed to help a HACCP or DAP team to think about what hazards or defects should be considered in the fresh fish, shellfish and other aquatic invertebrates, and then it is up to the team to determine the significance of the hazard or defect in relation to the process.
- (d) *Section 5 – Hazard Analysis Critical Control Point (HACCP) and Defect Action Point (DAP) Analysis* - Only when the groundwork in Section 3 has been satisfactorily achieved should the application of the principles outlined in *Section 5* be considered. This Section uses an example of the processing of a canned tuna product to help illustrate how the principles of HACCP should be applied to a process.
- (e) *Sections 6 and 7 – Aquaculture Production and Molluscan Shellfish production* deal with pre-harvest and primary production of fish, crustaceans and molluscan shellfish not caught in the wild*.

Although potential hazards and potential defects are listed for most steps in Sections 6 to 18, it should be noted that this is only for guidance and the consideration of other hazards and/or defects may be appropriate. Also, the format in these Sections has been designed for maximum ‘ease of use’ and therefore the ‘**potential hazards**’ or ‘**potential defects**’ are listed only where they may be introduced into a product or where they are controlled, rather than repeating them at all the intervening processing steps.

Additionally, it must be stressed that hazards and defects, and their subsequent control or action points, are product and line specific and therefore a full critical analysis based on *Section 5* must be completed for each individual operation.

- (f) *Section 8 - Processing of Fresh, Frozen and Minced Fish* – This Section forms the foundation for most of the subsequent processing Sections. It deals with the major process steps in the handling of raw fish through to cold storage and gives guidance and examples on the sort of hazards and defects to expect at the various steps. This Section should be used as the basis for all the other processing operations (Sections 9-16) which give additional guidance specific to the appropriate product sector*.

* Under development.

- (g) *Sections 9 to 16 – Processing of Specific Fish and Shellfish Products* – Processors operating in particular sectors will need to consult the appropriate Section to find additional information specific to that sector*.
- (h) *Sections 17 to 18 - Transportation and Retail* cover general transportation and retail issues. Transportation and retail apply to most if not all sections for processing of specific products. They should be considered with the same care as the other processing steps*.
- (i) Additional information will be found in the *Appendices**.

SECTION 1 - SCOPE

This Code of practice applies to the growing, harvesting, handling, production, processing, storage transportation and retail of fish, shellfish and aquatic invertebrates and products thereof from marine and freshwater sources, which are intended for human consumption.

SECTION 2 - DEFINITIONS

2.2 AQUACULTURE

Aquaculture	means the farming during part or the whole of their life cycle of all aquatic animals, except mammalian species, aquatic reptiles and amphibians intended for human consumption, but excluding species covered in section 7 of this code. These aquatic animals are hereafter referred to as “fish” for ease of reference in section 2.2 and section 6.
Aquaculture Establishment	is any premises for the production of fish intended for human consumption, including the supporting inner infrastructure and surroundings under the control of the same management.
Chemicals	includes any substance either natural or synthetic which can affect the live fish, its pathogens, the water, equipment used for production or the land within the aquaculture establishment.
Colouring	means obtaining specifically coloured feature (e.g. flesh/shell/gonad) of a targeted organism by incorporating into the fish food a natural or artificial substance or additive approved for this purpose by the agency having jurisdiction.
Diseased Fish	means a fish on or in which pathological changes or other abnormalities that affect safety and quality are apparent.
Extensive farming	means raising fish under conditions of little or incomplete control over the growing process and production conditions where their growth is dependent upon endogenously supplied nutrient inputs.
Feed Additives	means chemicals other than nutrients for fish which are approved for addition to their feed.
Fish farm	is an aquaculture production unit (either land-or water based); usually consisting of holding facilities (tanks, ponds, raceways, cages), plant (buildings, storage, processing), service equipment and stock.
Fish Feed	means fodder intended for fish in aquaculture establishments, in any form and of any composition.
Good Aquaculture (or Fish Farming)	are defined as those practices of the aquaculture sector that are necessary to produce quality and safe food products conforming to food laws and regulations

Practices

Harvesting	Operations involving taking the fish from the water.
Intensive farming	means raising fish under controlled growing process and production conditions where their growth is completely dependent on externally supplied fish feed.
Official Agency Having Jurisdiction	means the official authority or authorities charged by the government with the control of food hygiene (sometimes referred to as the competent authority) as well as/or with sanitation in aquaculture.
Pesticide	means any substance intended for preventing, destroying, attracting, repelling or controlling any pest including unwanted species of plants or animals during the production, storage, transport, distribution and processing of food, agricultural commodities, or animal feeds or which may be administered to animals for the control of ectoparasites. The term normally excludes fertilisers, plant and animal nutrients, food additives, and veterinary drugs.
Pesticide Residue	means any specified substance in food, agricultural commodities, or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities considered to be of toxicological significance.
Residues	means any foreign substances including their metabolites, which remain in fish prior to harvesting as a result of either application or accidental exposure.
Semi-intensive farming	means raising fish under conditions of partial control over the growing process and production conditions where their growth is dependent upon endogenously supplied nutrient inputs and externally supplied fish feed.
Stocking density	is the amount of fish stocked per unit of area or volume.
Veterinary Drug	means any substance applied or administered to any food-producing animal, such as meat or milk-producing animals, poultry, fish or bees, whether used for therapeutic, prophylactic or diagnostic purposes or for modification of physiological functions or behaviour.
Withdrawal Time	is the period of time necessary between the last administration of a veterinary drug to fish, or exposure of these animals to a veterinary drug, and harvesting of them to ensure that the concentration of the veterinary drug in their edible flesh intended for human consumption, complies with the maximum permitted residue limits.

SECTION 6 - AQUACULTURE PRODUCTION

Preamble

Aquaculture establishments should operate in a responsible way such that they comply with the recommendations of the Code of Conduct for Responsible Fisheries (FAO, Rome, 1995) in order to minimize any adverse impact on human health and environment including any potential ecological changes.

Fish farms should operate effective fish health and welfare management. Fry and fingerlings should be disease free and should comply with the OIE Codes of Practice (International Aquatic Animal Health Code, 6th Edition, 2003). Growing fish should be monitored for disease. When using chemicals at fish farms, special care should be exercised so that these substances are not released into the surrounding environment.

Whilst the fish health, environment, and ecological aspects are important considerations in aquaculture activities, this section focuses on food safety and quality aspects.

This Section of the Code applies to industrialised and commercial aquaculture production, producing all aquatic animals, except mammalian species, aquatic reptiles and amphibians for direct human consumption, but excluding bivalve molluscs covered in section 7 of the code, hereafter referred to as “fish that are intended for direct human consumption. Such intensive or semi-intensive aquaculture systems use higher stocking densities, stock from hatcheries, use mainly formulated feeds and may utilise medication and vaccines. This Code is not intended to cover extensive fish farming systems that prevail in many developing countries or integrated livestock and fish culture systems. This section of the code covers the feeding, growing, harvesting and transport stages of aquaculture production. Further handling and processing of fish are covered elsewhere in the code.

In the context of recognising controls at individual processing steps, this section provides examples of potential hazards and defects and describes technological guidelines, which can be used to develop control measures and corrective action. At a particular step only the hazards and defects, which are likely to be introduced or controlled at that step, are listed. It should be recognised that in preparing a HACCP and/or DAP plan it is essential to consult Section 5 which provides guidance for the application of the principles of HACCP and DAP analysis. However, within the scope of this Code of Practice it is not possible to give details of critical limits, monitoring, record keeping and verification for each of the steps since these are specific to particular hazards and defects.

The following example flow diagram will provide guidance to some of the common steps in aquaculture production. The flow chart is for illustrative purpose only. For implementation of HACCP principles, a complete and comprehensive flow chart has to be drawn up for each product. References correspond to relevant Sections of the Code.

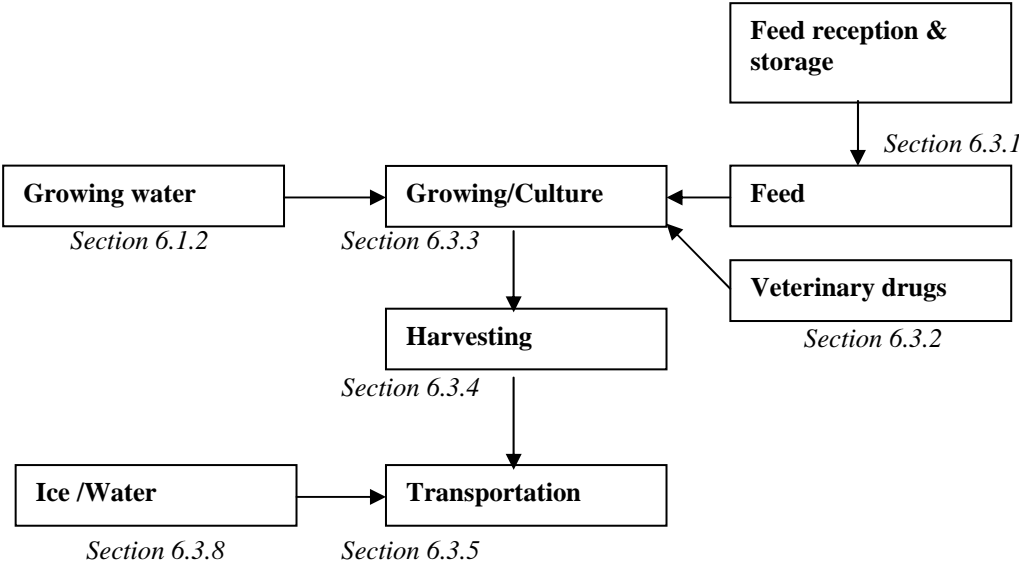


Figure 6.1 Example of a flow chart for aquaculture production

6.1 General

The general principles in Section 3 apply to aquaculture production, in addition to the following:

6.1.1 Site selection

- The siting, design and construction of fish farms should follow principles of good aquaculture practice, appropriate to species;
- The physical environment with regard to temperature, current, salinity and depth should also be considered since different species have different environmental requirements. Closed recirculation systems should be able to adapt the physical environment to the environment requirements of the farmed fish species;
- Fish farms should be located in areas where the risk of contamination by chemical, physical or microbiological hazards is minimal and where sources of pollution can be controlled;
- Soil for the construction of earthen ponds should not contain such concentrations of chemicals and other substances, which may lead to the presence of unacceptable levels of contamination in fish;
- Ponds should have separated inlets and discharge canals, so that water supplies and effluent are not mixed;
- Adequate facility for treatment of effluent should be provided to allow sufficient time for sediments and organic load settlement before used water is discharged into the public water body
- Water inlets and outlets to ponds should be screened to prevent the entrance of unwanted species;
- Fertilizers, liming materials or other chemicals and biological materials, should be used in accordance with good aquaculture practice;
- All sites should be operated so as to not adversely impact human health from the consumption of the fish in farm.

6.1.2 Growing Water Quality

- The water in which fish are raised should be suitable for the production of products which are safe for human consumption;
- The water quality should be monitored regularly such that the health and sanitation of the fish is continuously maintained to ensure aquaculture products are safe for human consumption;
- Fish farms should not be sited where there is a risk of contamination of the water in which fish are reared;
- Appropriate design and construction of fish farms should be adopted to ensure control of hazards and prevention of water contamination.

6.1.3 Source of Fry and Fingerlings

- The source of postlarvae, fries and fingerlings should be such to avoid the carryover of potential hazards into the growing stocks.

6.2 Identification of hazards and defects

Consumption of fish and fishery products can be associated with a variety of human health hazards. Broadly the same hazards are present in aquaculture products as in corresponding varieties caught in the wild (Section 4.1). The risk of harm from a particular hazard might be increased, under some circumstances, in aquaculture products compared with fish caught in the wild - for instance if the withdrawal time for residues of veterinary drugs has not been observed. High stocking densities, compared with the natural situation, might increase the risk of cross-infection of pathogens within a population of fish and might lead to deterioration of water quality. On the other hand, farmed fish can also present a lower risk of harm. In systems where the fish receive formulated feeds, the risks associated with transmission of hazards through the food consumed by the fish could be reduced. For example, infection with nematode parasites is absent from, or very much reduced in, farmed salmon compared with salmon caught in the wild. Raising fish in cages in the marine environment poses few hazards and low risks. In closed recirculation systems hazards are even further reduced. In those systems, the water is constantly refreshed and reused and water quality is controlled within safe measures.

6.2.1 Hazards

Aquaculture products possess broadly the same hazards that are present in corresponding varieties caught in the wild (Section 5.3.3.1). Potential hazards that are specific to aquaculture products include: residues of veterinary drugs in excess of recommended guidelines and other chemicals used in aquaculture production, contamination of faecal origin where the facilities are close to human habitation or animal husbandry.

6.2.2 Defects

The same defects are present in aquaculture products as in corresponding varieties caught in the wild (Section 5.3.3.1). A defect which may occur is objectionable odours/flavours. During transport of live fish, it is important to reduce stress, as stressing fish can lead to deterioration in quality. Also, care should be taken to minimise physical damage to fish as this can lead to bruising.

6.3 Production operations

6.3.1 Feed Supply

Feeds used in aquaculture production should comply with the Codex Recommended Code of Practice on Good Animal Feeding (CAC/RCP- 54 (2004)).

Potential Hazards: Chemical contamination, mycotoxins and microbiological contamination.

Potential Defects: Decomposed feeds, fungal spoilage

Technical Guidance:

- Feed and fresh stocks should be purchased and rotated and used prior to the expiry of their shelf life;
- Dry fish feeds should be stored in cool and dry areas to prevent spoilage, mould growth and contamination. Moist feed should be properly refrigerated according to manufacturers instructions;

- Feed ingredients should not contain unsafe levels of pesticides, chemical contaminants, microbial toxins, or other adulterating substances.
- Industrially produced complete feeds and industrially produced feed ingredients should be properly labelled. Their composition must fit the declaration on the label and they should be hygienically acceptable.
- Ingredients should meet acceptable, and if applicable, statutory standards for levels of pathogens, mycotoxins, herbicides, pesticides and other contaminants which may give rise to human health hazards.
- Only approved colours of the correct concentration should be included in the feed.
- Moist feed or feed ingredients should be fresh and of adequate chemical and microbiological quality.
- Fresh or frozen fish should reach the fish farm in an adequate state of freshness.
- Fish silage and offal from fish, if used, should be properly cooked or treated to eliminate potential hazards to human health
- Feed which is compounded industrially or at the fish farm, should contain only such additives, growth promoting substances, fish flesh colouring agents; anti-oxidising agents, caking agents or veterinary drugs which are permitted for fish by the official agency having jurisdiction.
- Products should be registered with the relevant national authority as appropriate.
- Storage and transport conditions should conform to the specifications on the label.
- Veterinary drug and other chemical treatments should be administered in accordance with recommended practices and comply with national regulations.
- Medicated feeds should be clearly identified in the package and stored separately, in order to avoid errors.
- Farmers should follow manufacturers' instructions on the use of medicated feeds.
- Product tracing of all feed ingredients should be assured by proper record keeping.

6.3.2 Veterinary Drugs

Potential Hazards: Residues of veterinary drugs

Potential Defects: Unlikely

Technical Guidance:

- All veterinary drugs for use in fish farming should comply with national regulations and international guidelines (in accordance with the Recommended International Code of Practice for Control of the Use of Veterinary Drugs (CAC/RCP 38-1993) and the Codex Guidelines for the Establishment of a regulatory programme for control of veterinary drugs residues in foods (CAC/GL 16-1993)).
- Prior to administering veterinary drugs, a system should be in place to monitor the application of the drug to ensure that the withdrawal time for the batch of treated fish can be verified.
- Veterinary drugs or medicated feeds should be used according to manufacturers' instructions, with particular attention to withdrawal periods.
- Products should be registered with the appropriate national authority.
- Products should only be prescribed or distributed by personnel authorised under national regulations.

- Storage and transport conditions should conform to the specifications on the label.
- Control of diseases with drugs should be carried out only on the basis of an accurate diagnosis
- Records should be maintained for the use of veterinary drugs in aquaculture production.
- For those fish which tested with drug residue concentrations above the MRL (or in some countries, by an industry imposed lower level), harvest of the batch should be postponed until the batch complies with the MRL. After an assessment of the Good Aquaculture Practices regarding pre-harvest measures, appropriate steps should be taken to modify the drug residue control system.
- A post harvest control should reject all fish that do not comply with the requirements set for veterinary drug residues by the relevant national authority.

6.3.3 Growing

Potential Hazards: Microbiological and chemical contamination

Potential Defects: Abnormal colour, muddy flavour, physical damage

Technical Guidance:

- Source of postlarvae, fries and fingerlings should be controlled to assure healthy stock.
- Stocking densities should be based on culture techniques, fish species, size and age, carrying capacity of the fish farm, anticipated survival and desired size at harvesting.
- Diseased fish should be quarantined when necessary and appropriate and dead fish should be disposed immediately in a sanitary manner that will discourage the spread of disease and the cause of death should be investigated.
- Good water quality should be maintained by using stocking and feeding rates that do not exceed the carrying capacity of the culture system.
- Growing water quality should be monitored regularly, so as to identify potential hazards and defects.
- The fish farm should have a management plan that includes a sanitation programme, monitoring and corrective actions, defined fallowing periods, appropriate use of agrochemicals, verification procedures for fish farming operations and systematic records.
- Equipment such as cages and nets should be designed and constructed to ensure minimum physical damage of the fish during the growing stage.
- All equipment and holding facilities should be easy to clean and to disinfect and should be cleaned and disinfected regularly and as appropriate.

6.3.4 Harvesting

Potential Hazards: Unlikely

Potential Defects: Physical damage, physical/biochemical change due to stress of live fish

Technical Guidance:

- Appropriate harvesting techniques should be applied to minimise physical damage and stress.

- Live fish should not be subjected to extremes of heat or cold or sudden variations in temperature and salinity.
- Fish should be free from excessive mud and weed soon after being harvested by washing it with clean seawater or fresh water under suitable pressure.
- Fish should be purged, where necessary, to reduce gut contents and pollution of fish during further processing.
- Fish should be handled in a sanitary manner according to the guidelines in Section 4 of the Code.
- Harvesting should be rapid so that fish are not exposed unduly to high temperatures.
- All equipment and holding facilities should be easy to clean and to disinfect and should be cleaned and disinfected regularly and as appropriate.

6.3.5 Holding and Transportation

Potential Hazards: *microbiological and chemical contamination*

Potential Defects: *physical damage, physical/biochemical change due to stress of live fish*

Technical Guidance:

- Fish should be handled in such a way as to avoid unnecessary stress.
- Fish should be transported without undue delay.
- Equipment for the transport of live fish should be designed for rapid and efficient handling without causing physical damage or stress.
- All equipment and holding facilities should be easy to clean and to disinfect and should be cleaned and disinfected regularly and as appropriate.
- Records for transport of fish should be maintained to ensure full product tracing.
- Fish should not be transported with other products which might contaminate them.

6.3.6 Storage and transport of live fish

This section is designed for the storage and transportation of live fish originating from aquaculture or capture.

Potential Hazards: *microbiological contamination, biotoxins, chemical contamination (e.g. oil, cleaning and disinfecting agents)*

Potential Defects: *Dead fish, physical damage, off flavours, physical/biochemical change due to stress of live fish*

Technical Guidance:

- Only healthy and undamaged fish should be chosen for live storage and transport. Damaged, sick and dead fish should be removed before introduction to the holding or conditioning tanks.
- Holding tanks should be checked regularly during storage and transportation. Damaged, sick and dead fish should be removed immediately when found.
- Clean water utilised to fill holding tanks, or to pump fish between holding tanks, or for conditioning fish, should be similar in properties and composition to the water from where the fish was originally taken to reduce fish stress.

- Water should not be contaminated with either human sewage or industrial pollution. Holding tanks and transportation systems should be designed and operated in a hygienic way to prevent contamination of water and equipment.
- Water in holding and conditioning tanks should be well aerated before fish is transferred into them.
- Where seawater is used in holding or conditioning tanks, for species prone to toxic algae contamination, seawater containing high level of cell concentrations should be avoided or filtered properly.
- No fish feeding should occur during storage and transport of live fish. Feeding will pollute water of holding tanks very quickly and, in general, fish should not be fed 24 hours before transporting.
- Material of holding and conditioning tanks, pumps, filters, piping, temperature control system, intermediate and final packaging or containers should not be harmful to fish or present hazards to humans.
- All equipment and facilities should be cleaned and disinfected regularly and as needed.

6.3.6.1 Live fish stored and transported at ambient temperature

Potential Hazards: microbiological contamination, biotoxins, chemical contamination (e.g. oil, cleaning and disinfecting agents)

Potential Defects: Dead fish, physical damage, off flavours, physical/biochemical change due to stress of live fish

Technical Guidance:

- Depending on the source of water, requirements of the species and time of storage and/or transport, it could be necessary to re-circulate the water and filter it through mechanical and/or biofilters.
- Water intake of holding tanks on board of vessels should be located so as to avoid contamination from vessel's sewage, waste and engine cooling discharge. Pumping of water should be avoided when the vessel comes into harbour or sailing through waters near sewage or industrial discharges. Equivalent precautions should be adopted for water intake on land.
- Facilities for storing and transportation (holding tanks) of live fish should be capable to:
 - maintain the oxygenation of water in the holding tanks through either, continuous water flow, direct oxygenation (with oxygen or air bubbling), or regularly and as needed changing of the water of the holding tank;
 - maintain the temperature of storage and transport, for species sensitive to temperature fluctuations. It may be necessary to insulate the holding tanks and install a temperature control system;
 - keep water in reserve which might be needed in case the holding tank should drain. The volume in fixed facilities (storage) should be at least of the same volume of the total holding tanks in operation. The volume in land transport facilities should be at least capable to compensate water for evaporation, leakage, purges, filter cleaning and eventual mixing of water for control purposes;

- For species known to exhibit strong territoriality or cannibalism or hyperactivity when under stress, these fish should be separated in individual tanks or appropriately secured/banned to prevent damage (an alternative method is reduction of temperature).

6.3.6.2 Live fish stored and transported at low temperatures

Potential Hazards: microbiological contamination, biotoxins, chemical contamination (e.g. oil, cleaning and disinfecting agents)

Potential Defects: Dead fish, physical damage, off flavours, physical/biochemical change due to stress of live fish

Technical Guidance:

- Conditioning should aim at reducing the metabolic rate of fish in order to minimize the stress to them. Conditioning of the fish at low temperatures should be done according to the characteristics of the species (minimum temperature, cooling rate, water/humidity requirements, packaging conditions). Conditioning is a biological operation to reduce the metabolic rate of the fish minimising the stress to them.
- The level of temperature to be reached should be in accordance with the species, transport and packaging conditions. There is a range of temperature in which fish do not exhibit or have reduced physical activity. The limit is attained at the temperature at which the metabolic rate of the fish is minimised without causing adverse effects to them (basal metabolic rate).
- When performing conditioning, only approved anaesthetics and procedures accepted by the regulations should be used.
- Conditioned fish should be packed without delay in proper insulated containers.
- Remaining water or water for use with packaging material for conditioned fish should be clean, of similar composition and pH to the water the fish was taken from, but to the temperature of storage.
- Water absorbent pads, shredded wood, wood shavings or sawdust and tying material that may be utilised for packaging conditioned fish should be clean, first use, free of possible hazards and be wet right at the time of packaging.
- Conditioned and packed fish should be stored or transported under conditions that assure proper temperature control.

Documents and links related to antimicrobial resistance and/or aquaculture from FAO, OIE, WHO and Codex

FAO Publications related to aquaculture and antimicrobial use:

Code of Conduct for Responsible Fisheries.

1995 41 pg

ISBN: 9251038341

::[Code of Conduct for Responsible Fisheries](#)

FAO, 2004. The State of Fisheries and Aquaculture.

ISBN: 9251051771g

2004 153 p

::[FAO, 2004. The State of Fisheries and Aquaculture \(Sofia\)](#)

FAO, 2006. Responsible use of Antibiotics in Aquaculture

ISBN 92-5-105436-3

::[FAO, 2006. Responsible use of Antibiotics in aquaculture \(T469\)](#)

Ottolenghi, F.; Silvestri, C.; Giordano, P.; Lovatelli, A.; New, M.B.

Capture-based aquaculture. The fattening of eels, groupers, tunas and yellowtails.

Rome, FAO. 2004. 308p.

::[FAO, 2004. Capture-based aquaculture, the fattening of eels, groupers, tuna and yellowtails](#)

FAO Fisheries Circular

No. 886, Rev. 2

2003 95 pg

::[FAO, 2003. Review of the state of world aquaculture \(2003\)](#)

GESAMP (IMO/FAO/UNESCO-IOC/WMO/WHO/IAEA/UN/UNEP Joint Group of Experts on the Scientific Aspects of Marine Environmental Protection).

Towards safe and effective use of chemicals in coastal aquaculture.

Reports and Studies, GESAMP. No. 65. Rome, FAO. 1997. 40 p.

::[Towards safe and effective use of chemicals in coastal aquaculture](#)

Arthur, J.R.; Phillips, M.J.; Subasinghe, R.P.; Reantaso, M.B.; MacRae, I.H. (eds.)

Primary Aquatic Animal Health Care in Rural, Small-scale, Aquaculture Development.

FAO Fisheries Technical Paper. No. 406. Rome, FAO. 2002. 382 p.

::[Primary aquatic animal health care in rural, small-scale aquaculture development](#)

FAO Fisheries Circular N. 973.

FIRI/C973.

Rome, 2001.

::[Production, Accessibility, Marketing and Consumption Patterns of Freshwater Aquaculture Products in Asia: A Cross-Country Comparison](#)

FAO TECHNICAL GUIDELINES FOR RESPONSIBLE FISHERIES

5, Suppl. 1

ISBN 92-5-104613-1

::[FAO, Aquaculture development. 1. Good aquaculture feed manufacturing practice.](#)

Aquaculture Development Beyond 2000:

The Bangkok Declaration and Strategy

Conference on Aquaculture Development in the Third Millennium

20-25 February 2000

Bangkok, Thailand
ISBN: 974-85935-1-17

::[Aquaculture Development Beyond 2000:](#)

Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL, Bangkok, Thailand,
24 - 26 August 2004

::[Residues of Veterinary Drugs without ADI/MRL](#)

FAO, 2003. Assessment and Management of Seafood Safety
ISBN 92-5-104954-8

::[FAO, 2003. Assessment and management of seafood safety and quality \(T444\)](#)

Committee on Fisheries
SUB-committee on Aquaculture
Second Session
Trondheim, Norway, 7-11 August 2003
Cofi:aq/ii/2003/6

::[Strategies to improve safety and quality of aquaculture products](#)

[Residues of veterinary drugs without ADI/MRL](#)
http://www.fao.org/ag/agn/food/risk_vetdrugs_en.stm

OIE Documents related to Antimicrobial Resistance

Terrestrial Animal Health Code (2006)

Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine

Link: http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.3.htm

Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals

Link: http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.4.htm

Guidelines for the harmonisation of antimicrobial resistance surveillance and monitoring programmes.

Link: http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.1.htm

Guidelines for the monitoring of the quantities of antimicrobials used in animal husbandry

Link: http://www.oie.int/eng/normes/mcode/en_chapitre_3.9.2.htm

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals: Laboratory methodologies for bacterial antimicrobial susceptibility testing

Link: http://www.oie.int/eng/normes/mmanual/A_00021.htm

Manual of Diagnostic Tests for Aquatic Animals

Link: http://www.oie.int/eng/normes/fmanual/A_summry.htm

Aquatic Animal Health Code (2006)

Link: http://www.oie.int/eng/normes/fcode/en_sommaire.htm

WHO Documents related to Antimicrobial Resistance

:: [Critically important antibacterial agents for human medicine: Report of a WHO working group consultation \[pdf 214kb\]](#)

Canberra, Australia, 15-18 February 2005

:: [Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management options](#)

Oslo, Norway, 15–18 March 2004, Ref: WHO/CDS/CPE/ZFK/2004.8

:: [First Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment](#)

Geneva, 1–5 December 2003, Ref: WHO/CDS/CPE/ZFK/2004.7

:: [WHO Consultation on Monitoring antimicrobial usage in food animals for the protection of human health](#)

Oslo, Norway, 10-13 September 2001, Ref: WHO/CDS/CSR/EPH/2002.11

:: [WHO Consultation on Global Principles For The Containment Of Antimicrobial Resistance In Animals Intended For Food](#)

with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties, Geneva, Switzerland 5-9 June 2000, Ref: WHO/CDS/CSR/APH/2000.4

:: [Use of Quinolones in Food Animals and Potential Impact on Human Health:](#)

Report and Proceedings of a WHO Meeting, Geneva, Switzerland, 2-5 June 1998, Ref: WHO/EMC/ZDI/98.12

:: [Use of Quinolones in Food Animals and Potential Impact on Human Health:](#)

Report of a WHO Meeting, Geneva, Switzerland, 2-5 June 1998, Ref: WHO/EMC/ZDI/98.10

:: [The Medical Impact of the Use of Antimicrobials in Food Animals: Report and Proceedings of a WHO Meeting](#)

Berlin, Germany, 13-17 October 1997, Ref: WHO/EMC/ZOO/97.4

:: [Report of the WHO Working Group on Antimicrobial Resistance](#)

Weybridge, United Kingdom, 4 December 1991, Ref: VPH/92.105

:: [Guidelines for Surveillance and Control of Antimicrobial Resistance](#)

Geneva, Switzerland, 1990, Ref: WHO/Zoonoses/90.167

Press release:

:: [WHO issues new recommendations to protect human health from antimicrobial use in food animals](#)

Press releases 2000, WHO/43 13 June 2000

Codex Documents related to Antimicrobial Resistance

Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005)
(http://www.codexalimentarius.net/download/standards/10213/CXP_061e.pdf)

Recommended International Code of Practice for Control of the Use of Veterinary Drugs CAC/RCP 38-1993
(http://www.codexalimentarius.net/download/standards/46/CXP_038e.pdf)