Annex 17. Item 6.6. – Draft Chapter 6.2. 'Responsible and prudent use of antimicrobial agents in aquatic animals'

CHAPTER 6.2.

~~PRINCIPLES FOR~~ RESPONSIBLE AND PRUDENT USE OF *ANTIMICROBIAL AGENT*S IN *AQUATIC ANIMAL*S

Norway	**Category:** General **Proposed amended text:** not relevant **Rationale:** Norway supports the thorough revision of this Chapter. This revised chapter significantly strengthens guidance on prudent and responsible use of antimicrobial agents in aquatic animals, aligning the content with current scientific knowledge and international best practices. Importantly, it offers a clear and well-structured overview of the roles and responsibilities of the various stakeholders. **Supporting evidence:** not relevant

Article 6.2.1.

Purpose

~~These principles provide guidance for the responsible and prudent use of *antimicrobial agents* in *aquatic animal*s, with the aim of protecting both animal and human health. The *Competent Authorities* responsible for the registration and marketing authorisation of products and the control of all organisations involved in the production, distribution and use of *antimicrobial agent*s have specific obligations.~~

To provide recommendations for the responsible and prudent use of *antimicrobial agent*s in veterinary medicine for treatment and control of *diseases* in *aquatic animals* for human consumption (food-producing *aquatic animal*s) and for other purposes (non-food producing *aquatic animals*), with the aim of protecting both animal and human health as well as minimising and containing antimicrobial resistance *risks* in the relevant aquatic environment, as part of a One Health approach.

Article 6.2.2.

~~**Objectives of responsible and prudent use**~~

~~Responsible and prudent use includes a set of practical measures and recommendations intended to reduce the *risk* associated with the selection and dissemination of antimicrobial resistant microorganisms and antimicrobial resistance determinants in *aquatic animal* production to:~~

~~1. maintain the efficacy of *antimicrobial agent*s both for veterinary and human medicine and to ensure~~

~~the rational use of antimicrobials in *aquatic animals* with the purpose of optimising both their efficacy and safety;~~

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

~~3. prevent or reduce the transfer of both resistant microorganisms and resistance determinants from *aquatic animals* to humans and terrestrial animals;~~

~~4. prevent antimicrobial residues that exceed the established maximum residue limit (MRL) occurring in the food.~~

Scope

This chapter describes recommendations on responsible and prudent use of *antimicrobial agent*s for *Competent Authorities* and stakeholders such as the veterinary pharmaceutical industry, *veterinarians* and *aquatic animal health professionals*, aquatic animal feed manufacturers, distributors, and aquatic animal producers, owners and keepers, who are involved in any or all of the following activities: regulatory approval, production, control, importation, exportation, sales, advertising, distribution, prescription and use of *antimicrobial agent*s

Article 6.2.3.

~~**Definition**~~

~~**Pharmacovigilance of *antimicrobial agent*** means the detection and investigation of the effects of the use of these products, mainly aimed at safety and efficacy in *aquatic animals* and safety in people exposed to the products~~

Introduction

Responsible and prudent use is determined by the importance of the *antimicrobial agent* to veterinary and human medicine, the *risk* of development of antimicrobial resistance, the specifications detailed in the relevant regulatory approval and the indications for use, including off-label use when *antimicrobial agent*s are administered to *aquatic animals*. It is part of good veterinary practice.

Measures to keep aqu*atic animals* healthy, such as good husbandry practices that minimize stress and provide a suitable rearing environment and *biosecurity* measures (in accordance with Chapter 4.1.) contribute to a decreased need of using *antimicrobial agent*s in aqu*atic animals*, thereby reducing the *risk* of the development and spread of antimicrobial resistance.

Activities associated with the responsible and prudent use of *antimicrobial agent*s should involve all relevant stakeholders. Coordination of these activities at the national or regional level is recommended and may support the implementation of targeted actions by the stakeholders involved and enable clear and transparent communications.

Article 6.2.~~2~~.4.

Objectives of responsible and prudent use

~~Responsible and prudent use includes a set of practical measures and recommendations intended to reduce the *risk* associated with the selection and dissemination of antimicrobial resistant microorganisms and antimicrobial resistance determinants in aquatic animal production to:~~

The objectives of responsible and prudent veterinary medical use of *antimicrobial agents* are to:

1. maintain the efficacy of *antimicrobial agents* both for veterinary and human medicine and to ensure the rational use of *antimicrobial agents* in *aquatic animals* with the purpose of optimising both their efficacy and safety;

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

3. prevent or reduce the transfer of both resistant microorganisms and resistance determinants within *aquatic animal* populations and between animals, humans and the environment;

4. ~~prevent antimicrobial residues that exceed the established maximum residue limit (MRL) occurring in the food~~ protect human health by ensuring the safety of food of *aquatic animal* origin with respect to residues of *antimicrobial agent*s

To achieve these objectives, a range of measures intended to improve the health of aquatic animals for human consumption and for other purposes (i.e. non-food producing aquatic animals) should be implemented. These measures include implementation of good husbandry practices, *biosecurity plans*, early *disease* detection and alternatives to the use of antimicrobials, which can help to minimise the need for antimicrobial use in *aquatic animal*s.

Article 6.2.5

General Principles

The general principles to achieve responsible and prudent veterinary medical use of *antimicrobial agent*s are:

1. *Competent Authorities* shall ensure an independent, science-based regulatory framework for *antimicrobial agents* in *aquatic animals*, applying a One Health approach to minimise antimicrobial resistance, as described in Article 6.2.6.
2. The veterinary pharmaceutical industry shall ensure *antimicrobial agents* meet approved quality, safety and efficacy standards and support stewardship through responsible promotion and pharmacovigilance, as described in Article 6.2.7.
3. Wholesale and retail distributors shall distribute *antimicrobial agents* in compliance with legislation, ensuring proper information, record-keeping and traceability, as described in Article 6.2.8.
4. *Veterinarians* and authorised *aquatic animal health professionals* shall practise evidence-based antimicrobial stewardship, prioritising prevention and regulatory compliance, as described in Article 6.2.9.
5. Animal feed manufacturers shall produce and supply medicated feed under veterinary prescription, in compliance with legislation and good manufacturing practices, ensuring safe and traceable use, as described in Article 6.2.10.
6. *Aquatic animal* producers shall implement effective health and *biosecurity* programmes and use *antimicrobial agents* only under authorised prescription with proper record-keeping, as described in Article 6.2.11.
7. Owners and keepers of aquatic animals not intended for human consumption shall, under professional guidance, implement health and *biosecurity* measures to reduce antimicrobial use, as described in Article 6.2.12.
8. All stakeholders shall ensure appropriate training to promote responsible antimicrobial use, stewardship and effective monitoring, as described in Article 6.2.13.
9. *Competent Authorities* and stakeholders shall promote coordinated One Health research and innovation to address knowledge gaps and develop alternatives to antimicrobial use, as described in Article 6.2.14.

Article 6.2.4.~~6~~.

Responsibilities of Competent Authorities

1. National Action Plan on Antimicrobial Resistance

Competent Authorities should design and oversee the implementation of the parts of their National Action Plan relevant to their responsibilities, considering the findings of the situational analysis of the country, the objectives of the WOAH, WHO, FAO and UNEP Global Action Plan (GAP) for Antimicrobial Resistance and existing guidance for developing National Action Plans for antimicrobial resistance. *Competent Authorities* in cooperation with animal health, plant health, environment and public health professionals, and other relevant stakeholders should adopt a One Health approach to promote the responsible and prudent use of *antimicrobial agent*s as an element of a national strategy to minimise and contain antimicrobial resistance. Furthermore, *Competent Authorities* should allocate budgetary resources for the design and implementation of the parts of their National Action Plan relevant to their responsibilities including communication strategies and professional training programmes. The *Competent Authorities* should also conduct regular monitoring and evaluation of the National Action Plan.

National Action Plans should incorporate and inform best management practices, including *disease* prevention and control measures and implementation of *biosecurity* and *aquatic animal* health programmes to reduce the burden of *aquatic animal diseases* thereby reducing the need for antimicrobial use. As part of National Action Plans, *Competent Authorities* should ensure that monitoring for antimicrobial use and antimicrobial resistance in the *aquatic animal* health sector is in place and should work closely together with human and other relevant sectors on the harmonisation, analysis and integration of monitoring. The *Competent Authorities* should implement a programme in accordance with Chapters 1.4. and 6.4.

National Action Plans should include recommendations on specific tasks for relevant professional organisations to develop evidence-based species or sector-specific antimicrobial use guidelines.

2. Regulatory approval

A *Competent Authority* must be responsible for granting relevant regulatory approval for antimicrobial use in aquatic animals which should be done in accordance with the provisions of the Aquatic Code. The *Competent Authority* has a significant role in specifying the terms of this approval and in providing the appropriate information to *veterinarians*, authorized *aquatic animal health professionals*, and all other relevant stakeholders.

The *Competent Authority* should establish and implement efficient statutory registration procedures that evaluate the quality, safety and efficacy and post-marketing monitoring programmes for veterinary medicinal products containing *antimicrobial agents*. In accordance with Article 3.1.2., the *Competent Authority* should be free from any commercial, financial, hierarchical, political or other pressures which might influence its judgement or decisions.

Member Countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicinal products containing *antimicrobial agents*, and which are importing them, should undertake the following measures:

a. Evaluate the effectiveness of administrative controls on the import of these veterinary medicinal products;

b. Evaluate the validity of the registration procedures of the exporting or manufacturing country as appropriate;

c. Develop the necessary technical co-operation with an experienced *Competent Authority* to check the quality of imported veterinary medicinal products as well as the validity of the recommended conditions of use.

The *Competent Authority* of importing countries should request the veterinary pharmaceutical industry to provide certificates of quality prepared by the *Competent Authority* of the exporting or manufacturing country as appropriate.

Regulatory approval is granted for veterinary medical use on the basis of the data submitted by a pharmaceutical company or other applicant and only if the criteria of quality, safety and efficacy are met.

The *Competent Authority* is encouraged to consult and apply, as appropriate, the guidelines based on the technical requirements for veterinary product registration established by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

An evaluation of the *risks* and benefits to both animals and humans resulting from the use of *antimicrobial agents* in *aquatic animals* should be carried out. The evaluation may focus on each individual *antimicrobial agent;* the findings from one agent should not be generalised to the antimicrobial class to which the particular active ingredient belongs. Guidance on use should be provided for all target species, route of administration, dosage regimen (dose, dosing interval and duration of the administration), and withdrawal period as relevant.

The *Competent Authority* should implement timely regulatory approval processes for new *antimicrobial agents* or other options, including alternatives to the use of antimicrobials, in order to address specific needs for the treatment of *aquatic animal diseases* and should take into account recommendations included in the WOAH List of Antimicrobials of Veterinary Importance.

3. Quality of *antimicrobial agents* and veterinary medicinal products containing *antimicrobial agents*

The *Competent Authority* should make sure that the quality of the veterinary medicinal products was determined by the applicant in accordance with national and international guidance to ensure that:

a. The specifications of *antimicrobial agents* used as active ingredients comply with the provisions of registration documentations (such as monographs) approved by the relevant *Competent Authority;*

b. The quality of *antimicrobial agents* in the marketed dosage forms is maintained until the expiry date, established under the recommended storage conditions;

c. *Antimicrobial agents* are stable and compatible when mixed with feed or water, where permitted by the national regulation;

d. All *antimicrobial agents* and the veterinary medicinal products containing them are manufactured to the appropriate quality and in compliance with the provisions of good manufacturing practices.

4. Assessment of efficacy

The *Competent Authority* should conduct an assessment of the efficacy based on data provided in the relevant regulatory approval application submitted by the applicant to enable marketing:

a. Preclinical trials

i. Preclinical trials should:

- establish the spectrum of activity of *antimicrobial agents* against relevant *pathogenic agents* and non-pathogenic agents (commensals);

- assess the capacity of the *antimicrobial agents* to select for resistance *in vitro* and *in vivo*, taking into consideration intrinsically resistant strains and strains with acquired resistance;

- establish an appropriate dosage regimen and route of administration necessary to ensure the efficacy of the *antimicrobial agents* and limit the selection of antimicrobial resistance. Pharmacokinetic and pharmacodynamic data and models can assist in this appraisal. Such data together with clinical data could be used by independent experts to establish clinical breakpoints per *aquatic animal* species, *antimicrobial agent* and *pathogenic agent* combination. Data from standard setting organisations like CLSI and EUCAST should also be considered.

ii. The activity of *antimicrobial agents* towards the targeted microorganism should be established by pharmacodynamic investigations. The following characteristics should be taken into account, as appropriate:

- Spectrum of activity and mode of action;

- Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) against recent isolates;

- Time-kill kinetics;

- Time-dependent or concentration-dependent activity, or co-dependency;

- Activity and concentration at the site of *infection*.

iii. The dosage regimens allowing maintenance of effective antimicrobial concentrations should be informed by pharmacokinetic and pharmacodynamics investigations and should take into account:

- Any potential routes of administration proposed by the applicant;

- Absorption, distribution, metabolism and elimination, and concentration at the site of *infection*.

Further dose determination studies may be conducted to examine the microbiological and clinical response to several dose levels or dosing intervals.

Any proposed use of combinations of *antimicrobial agents* should be scientifically supported.

b. Clinical trials

Clinical trials in the target *aquatic animal* species should be performed to confirm the validity of the claimed indications and dosage regimens established during the preclinical phase. The following criteria should be taken into account:

- Diversity of the clinical *cases* encountered when performing multi-centre trials;

- Compliance of protocols with good clinical practice;

- Eligibility of studied clinical *cases*, based on appropriate criteria of clinical and bacteriological diagnoses;

- Parameters for qualitatively and quantitatively assessing the efficacy of the treatment and impact on the aquatic environment.

5. Assessment of the potential of *antimicrobial agents* to select for resistance

Other studies may be requested in support of the assessment of the potential of *antimicrobial agents* to select for resistance. The applicant for regulatory approval should, where possible, supply data derived in target *aquatic animal* species under the intended conditions of use.

For this assessment the following may be considered:

a. The concentration of active *antimicrobial agents* and, where appropriate, active metabolites in the gut, skin and gill mucus of the *aquatic animal* (where the majority of pathogenic and commensal bacteria reside) at the defined dosage level and discharged into the water;

b. The antimicrobial activity of the *antimicrobial agents* and metabolites in the intestinal environment and discharged into the water;

c. The pathway for human exposure to antimicrobial resistant microorganisms, antimicrobial resistance determinants and antimicrobial residues in the relevant *aquatic animal* production environment;

d. The presence of and potential for co-selection, co-resistance and cross-resistance;

e. The baseline level of resistance, including intrinsic and acquired resistance, in the pathogenic, commensal and food-borne bacteria of human health relevance in both *aquatic animals* and humans.

6. Assessment of the impact on the relevant *aquatic animal* production environment

The *Competent Authority* should consider the results of an antimicrobial resistance environmental *risk* assessment in accordance with Chapter 6.5. For both food- and non-food producing *aquatic animals* the *risk* factors for acquisition and transmission of AMR should be taken into consideration. For example: reuse of wastewater for irrigation, use of manure from terrestrial animals, use of sludge and other waste-based fertilisers for soil fertilisation, that could lead into transfer and spread of antimicrobial resistant microorganisms and determinants. When a significant antimicrobial resistance *risk* is determined the need for monitoring and proportionate *risk* management measures should be discussed.

7. Establishment of acceptable daily intake (ADI), maximum residue limit (MRL) and withdrawal periods in *aquatic animals* and *aquatic animal products* for human consumption

a. The establishment of an ADI for each *antimicrobial agent*, and an MRL for each *aquatic animal product* for human consumption, should be undertaken before a veterinary medicinal product containing an *antimicrobial agent* is granted regulatory approval. National MRLs may be harmonised with Codex MRLs and in cases where Codex MRLs do not exist, the procedure outlined in Codex Procedural Manual may be followed to determine National MRLs

b. When setting the ADI and MRL for an *antimicrobial agent*, the safety evaluation should also include the potential microbiological effects on the intestinal microbiota of humans to derive ADI.

c. For all veterinary medicinal products containing *antimicrobial agents* for use in *aquatic animals* for human consumption, withdrawal periods should be established for each *aquatic animal* species in order to ensure compliance with the MRLs, taking into account:

- the MRLs established for the *antimicrobial agent* in the target *aquatic animal* edible tissues;

- the composition of the product and the pharmaceutical form;

- the dosage regimen;

- the route of administration.

d. Methods used for regulatory testing of residues in food should be described and based on the established marker residues.

8. Establishment of a summary of product characteristics or equivalent for each veterinary medicinal product containing *antimicrobial agents*

The *Competent Authority* should ensure that the Summary of Product Characteristics (SPC) or equivalent, the package insert, and labelling includes the information necessary for the appropriate use of veterinary medicinal products containing *antimicrobial agents*. The SPC or equivalent summary should contain the following items as appropriate:

a. Name of the veterinary medicinal product;

b. Active ingredient and class;

c. Pharmaceutical form;

d. Quantitative composition;

e. Pharmacological properties;

f. Any potential adverse effects;

g. Target *aquatic animal* species and, as appropriate, age or production category;

h. Therapeutic indications;

i. Target microorganisms;

j. Dosage regimen (i.e. dose, frequency of dosing, and route and duration of administration) ;

k. Withdrawal periods;

l. Incompatibilities and interactions;

m. Storage conditions and shelf-life;

n. Operator safety;

o. Particular precautions before use;

p. Precautions for the protection of the environment including water stability;

q. Use in gravid *aquatic animals* and *eggs* ;

r. Particular precautions for the proper disposal of unused or expired products;

s. Information on conditions of use relevant to minimise the development of resistance;

t. Contraindications;

u. Known signs of overdosage and information about its treatment.

9. Post-marketing antimicrobial resistance monitoring

The *Competent Authority* should assess the information collected through existing pharmacovigilance and monitoring programmes, including reporting of lack of response, and any other relevant scientific data. These information sources should form part of the comprehensive strategy to detect and minimise antimicrobial resistance.

In addition, specific monitoring should be considered to assess the impact of the use of a specific veterinary medicinal product, where scientific evidence indicates a specific *risk* and may be implemented after the granting of the relevant regulatory approval. The monitoring programme should evaluate not only resistance in target *aquatic animal pathogenic agents*, but also in foodborne and other relevant zoonotic pathogens, and commensals if relevant and possible. This will also contribute to general epidemiological monitoring of antimicrobial resistance.

10. Distribution and administration of *antimicrobial agents* or veterinary medicinal products containing *antimicrobial agents*

The *Competent Authority* should ensure that all the *antimicrobial agents* in *aquatic animals* and medicated feed and water, where permitted, are:

a. supplied only through licensed or authorised distribution systems.

b. not illegal, substandard, falsified medicines or unapproved formulations and that these are prevented from entering distribution systems.

c. prescribed by a *veterinarian* or *aquatic animal health professiona*l authorised to prescribe veterinary medicinal products containing *antimicrobial agents* in accordance with the national legislation.

d. administered to *aquatic animals* under the supervision or by direction of a *veterinarian* or other authorised *aquatic animal health professional* as appropriate.

The *Competent Authority* should encourage the availability of authorised products on the market and in collaboration with the veterinary pharmaceutical industry follow-up any potential drug shortages.

Competent Authorities and stakeholders should work together to develop and implement effective procedures for the safe collection, transportation and disposal of unused or expired veterinary medicinal products containing *antimicrobial agents*. Their labels should have appropriate instructions for disposal and destruction.

11. Control of advertising

All advertising of *antimicrobial agents* should be compatible with the principles of responsible and prudent use and should be controlled by codes of advertising standards. *Competent Authorities* should aim to ensure that:

a. the advertising of these products complies with the regulatory approval granted, in particular regarding the content of the summary of product characteristics or equivalent;

b. advertising is restricted to a *veterinarian* or *aquatic animal health professional* authorised to prescribe veterinary medicinal products containing *antimicrobial agents*, or to persons permitted to supply veterinary medicinal products in accordance with the national legislation; and

c. their promotion is done in a manner consistent with specific regulatory recommendations for the product.

12. Establishing clinical breakpoints

The *Competent Authority* should encourage and support the development of clinical breakpoints for each bacteria-antimicrobial-*aquatic animal* species combination to interpret the results of susceptibility tests. EUCAST procedures could be used as guidance.

13. Training related to the use of *antimicrobial agents* and antimicrobial resistance

The *Competent Authority* should take a key role in promoting targeted training for responsible and prudent use of antimicrobials and on antimicrobial resistance. The target audiences for training on the use of *antimicrobial agents* should include all the relevant stakeholders and organisations, such as the veterinary pharmaceutical industry, veterinary education establishments and establishments of education for *aquatic animal health professionals*, research institutes, veterinary professional and *aquatic animal health professional* organisations, manufacturers of medicated feed, and other approved users such as breeders, owners and keepers of *aquatic animals*. The training may include the points described in Article 6.2.13.

14. Monitoring of antimicrobial use

In accordance with Chapter 6.3., the *Competent Authority* should collate data on antimicrobial use in a harmonised manner to improve the understanding of the extent and trends of antimicrobial use and antimicrobial resistance in *aquatic animal* populations at national level and identify areas for further research. The data collected on antimicrobial use at country level should:

a. give an indication of the trends in the use of *antimicrobial agents* in *aquatic animals* over time and potential associations with antimicrobial resistance in *aquatic animals*;

b. help in the interpretation of antimicrobial resistance monitoring data and assist in responding to problems of antimicrobial resistance in a precise and targeted way;

c. assist in *risk* management to evaluate the effectiveness of efforts and mitigation strategies;

d. inform *risk* communication strategies;

e. foster improved antimicrobial stewardship, ensuring continued availability of safe and effective *antimicrobial agents* for animal and human health.

The *Competent Authority* should provide the data to the 'Animal Antimicrobial Use Global database of the World Organisation for Animal Health' on a yearly basis.

15. Knowledge gaps and research

The *Competent Authority* should encourage coordination of public- and private-funded research, including in the areas described in Article 6.2.14.

16. *Competent Authorities* should implement appropriate regulatory measures to control the manufacture, compounding, importation, advertisement, trade, distribution, storage and use of unlicensed, adulterated and counterfeit veterinary medicinal products containing *antimicrobial agents*, including bulk active ingredients.

Article 6.2.~~5~~.7

Responsibilities of the veterinary pharmaceutical industry

The veterinary pharmaceutical industry has responsibilities for providing information requested by *Competent Authorities* on the quality, efficacy and safety of *antimicrobial agents*. The responsibilities of the veterinary pharmaceutical industry cover pre- and post-marketing phases, including manufacturing, sale, importation, labelling, advertising and pharmacovigilance.

The veterinary pharmaceutical industry has the responsibility to provide the *Competent Authority* with the information necessary to evaluate the amount of *antimicrobial agent*s marketed. ~~The veterinary pharmaceutical industry should ensure that the advertising of antimicrobial agents directly to the *aquatic animal* producer is discouraged.~~

The veterinary pharmaceutical industry has responsibility to implement, and report in a timely manner, a pharmacovigilance programme, and on request, specific monitoring for bacterial susceptibility data. For the latter, the veterinary pharmaceutical industry should isolate and identify bacteria and collect relevant data and submit them to the *Competent Authority*. These data may enable independent experts to establish clinical breakpoints for use in the laboratory to guide antimicrobial therapy.

The veterinary pharmaceutical industry should respect principles of responsible and prudent use and should comply with established codes of advertising practices, including to: distribute information in compliance with the provisions of the granted approval; not advertise veterinary medicinal products containing *antimicrobial agents* directly to *aquatic animal* producers, owners and keepers or to the general public.

Article 6.2.~~6~~.8.

Responsibilities of wholesale and retail distributors

Distributors should ensure that their activities are in compliance with the relevant legislation.

Distributors should ensure that information for the appropriate use and disposal of the *antimicrobial agent* accompany all distributed products and should also be responsible for maintaining and disposing of the product in accordance with the manufacturer recommendations.

The recommendations on the responsible and prudent use of *antimicrobial agents* should be reinforced by retail distributors who should keep for an appropriate period detailed sales record of:

a. date of sale;

b. name and contact information of the prescriber;

c. name of user;

d. name of product;

e. batch number;

f. expiration date;

g. quantity supplied;

h. copy of prescription or equivalent;

i. other information as required by national legislation.

Article 6.2.~~7~~.9.

Responsibilities of *veterinarians* ~~and~~ or ~~other~~ authorised *aquatic animal health professionals*

The *veterinarian*'s and authorised *aquatic health professional*'s responsibility is to promote *aquatic animal* health and *aquatic animal* welfare, as well as public health, through antimicrobial stewardship, prevention, detection, *diagnosis*, control and treatment of *aquatic animal diseases*. The promotion of sound aquatic animal husbandry methods, hygiene procedures, *biosecurity* and vaccination strategies can help to minimise the need for agent antimicrobials use in *aquatic animal*s.

Responsibilities of *veterinarians* or authorised *aquatic animal health professionals* include identifying, preventing and treating *aquatic animal diseases*, as well as the promotion of sound animal husbandry methods, hygiene procedures, vaccination and other alternative strategies to minimise the need for antimicrobial use in *aquatic animal*s.

~~*Veterinarians* or other *aquatic animal health professionals* authorised to prescribe veterinary medicines should only prescribe, dispense or administer a specific course of treatment with an *antimicrobial agent* for *aquatic animals* under their care.~~

The *veterinarian* or authorised *aquatic animal health professional* should consider safe and effective alternatives to the use of antimicrobials before prescribing *antimicrobial agents*.

1. Pre-requisites for using *antimicrobial agent*s

The responsibilities of *veterinarians* and other *aquatic animal health professionals* are to obtain a detailed history and carry out a ~~thorough~~ proper clinical ~~assessment~~ examination of the *aquatic animal*(s), including as appropriate: clinical examination, post-mortem examination, bacteriology with culture and ~~sensitivity~~ antimicrobial susceptibility, and other laboratory tests to arrive at the most definitive *diagnosis* possible before initiating a specific course of treatment with an *antimicrobial agent*. Evaluation of environmental factors and husbandry at the ~~production site~~ *aquaculture establishment* (e.g. water quality) should be considered as potential primary factors leading to *infection* and should be addressed prior to prescribing a course of *antimicrobial agent* treatment. If the provisional or definitive *diagnosis* is a microbial *infection*, then the *veterinarian* and other *aquatic animal health professional*, should:

a. prescribe, dispense or administer *antimicrobial agent*s only when necessary to treat or control infectious *diseases* in *aquatic animal*s;

b. if therapy with an *antimicrobial agent* is deemed necessary it should be initiated as soon as possible;

c. avoid the use of *antimicrobial agent*s to compensate for inadequate *aquatic animal* husbandry practices;

d. take into consideration the WOAH List of *Antimicrobial agent*s of Veterinary Importance and follow science-based species or sector-specific antimicrobial use guidelines for responsible and prudent use when available and follow the principles of antimicrobial stewardship;

e. make an appropriate choice of *antimicrobial agent* based on clinical experience and available diagnostic laboratory information (*pathogenic agent* isolation, identification and antimicrobial susceptibility testing);

f. provide a detailed treatment protocol, including precautions and withdrawal period (if applicable), especially when prescribing extra-label or off-label use.

~~The selection of the agent should be based on the knowledge and experience of the *veterinarian* or other *aquatic animal health professional* authorised to prescribe veterinary medicines.~~

~~As soon as possible, susceptibility testing of the target microorganism should be used to confirm the choice of treatment. Results of all susceptibility tests should be retained and should be available to the *Competent Authority*.~~

2. Choosing *antimicrobial agent*s

The choice of an effective treatment is based on:

a. the clinical experience of the *veterinarians* and authorised *aquatic animal health professionals*, their diagnostic insight and therapeutic judgement;

b. diagnostic laboratory information (*pathogenic agent* isolation, identification and antimicrobial susceptibility testing);

c. pharmacodynamic properties of the selected *antimicrobial agent*, including the activity towards the *pathogenic agents* involved;

d. the appropriate dosage regimen (i.e. dose, frequency of dosing, and route and duration of administration);

e. pharmacokinetics and tissue distribution to ensure that the selected therapeutic agent is effective at the site of *infection*;

f. the epidemiological history relevant to the *aquatic animal* or animals being treated, particularly in relation to the antimicrobial resistance profiles of the *pathogenic agents* involved.

Should a first-line antimicrobial treatment fail or should the *disease* recur, an investigation should be undertaken to reassess the circumstances including reviewing the *diagnosis*, conducting additional diagnostic testing as needed, and then formulate and implement a new treatment plan, which may or may not include another *antimicrobial agent*.

3. Appropriate veterinary medical use of the selected product containing *antimicrobial agent*s

The prescription of an *antimicrobial agent*s should indicate the dosage regimen, the withdrawal period where applicable, and when considering group treatments, the total amount of veterinary medicinal products containing *antimicrobial agent*s to be provided, which will depend on the dosage, duration of treatment, and the number of animals to be treated.

The *veterinarian* or authorised *aquatic animal health professionals* should ensure that instructions for the administration of the product are clearly explained and understood by producers or any other person responsible for administering the product. The *veterinarian* or other *aquatic animal health professional* authorised to prescribe veterinary medicines should indicate precisely to the *aquatic animal* producer the treatment regime, including the dose, the treatment intervals, the duration of the treatment, the withdrawal period (if appropriate) and the amount of *antimicrobial agent*s to be delivered, depending on the dosage and the number of *aquatic animals* to be treated.

The use of ~~*antimicrobial agents*~~ extra-label~~/~~ or off-label use of an *antimicrobial agent* may be permitted in certain appropriate circumstances and should be for treatment and control of *diseases*, in ~~conformity~~ agreement with the ~~relevant~~ national legislation in force including the withdrawal period, as applicable. It is the *veterinarian*'s responsibility to define the conditions of responsible and prudent use in such a case including the dosage regimen, the route of administration and the withdrawal period.

The use of *antimicrobial agent*s and extra-label or off-label use of registered veterinary medicinal products containing *antimicrobial agent*s should be limited to circumstances where an appropriate registered product is not available and should take into account recommendations provided in the WOAH List of *Antimicrobial Agents* of Veterinary Importance.

~~Records on the use of antimicrobial agents should be kept in conformity with the relevant legislation. *Veterinarians* or *aquatic animal health professionals* should also periodically review farm records on the use of the antimicrobial agents to ensure compliance with their directions and use these records to evaluate the efficacy of treatment regimens. Suspected adverse reactions, including a lack of efficacy, should be reported to the *Competent Authority*. Associated susceptibility data should accompany the report of lack of efficacy.~~

4. Recording of data

Records of veterinary medicinal products containing *antimicrobial agent*s should be kept in conformity with the national legislation. Records should include the following, as appropriate:

a. commercial name of the veterinary medicinal products;

b. name of the *antimicrobial agent*s in the veterinary medicinal products;

c. quantities used in animals or supplied to each *aquaculture establishment* or animal breeder, owner or keeper;

d. route of administration;

e. *aquatic animal* species;

f. number of *aquatic animals* treated;

g. clinical condition treated;

h. treatment schedules including *aquatic animal* identification and length of the withdrawal period;

i. laboratory records of *pathogenic agent* isolation, identification and susceptibility testing; such records should also be shared with the *aquatic animal* producers

j. comments concerning the response of the *aquatic animals* to treatment;

k. the investigation of adverse reactions associated with antimicrobial treatment, including lack of effectiveness. Suspected adverse reactions should be reported to the holder of the regulatory approval or appropriate *Competent Authority* in accordance with national legislation.

Veterinarians and other *aquatic animal health professionals* should also periodically review *aquaculture establishment* records on the use of veterinary medicinal products containing *antimicrobial agents* to ensure compliance with their directions or prescriptions and use these records to evaluate the effectiveness of treatments.

5. Labelling

All veterinary medicinal products containing *antimicrobial agent*s, supplied by a *veterinarian* or authorised *aquatic animal health professionals* should be labelled in accordance with the national legislation.

Article 6.2.10

Responsibilities of aqua*tic animal* feed manufacturers

Aquatic animal feed manufacturers preparing medicated feed should:

1. Only manufacture and supply medicated *feed* containing *antimicrobial agent*s for aquatic animals on the prescription of a *veterinarian* or authorised *aquatic animal professional* in accordance with the national legislation.

2. Prepare medicated *feed* containing *antimicrobial agent*s following rules put in place by the *Competent Authority* in accordance with the national legislation. All medicated *feed* and medicated premixes should be appropriately labelled.

3. Keep detailed records for medicated *feed* and premixes for a suitable period of time according to national legislation.

4. Add only approved sources of pharmaceutical products to *feed* at a level, and for a species and purpose as permitted by the medicated premix label or a veterinary prescription or equivalent.

5. Ensure medicated *feed* containing *antimicrobial agent*s is labelled with the appropriate information (e.g., level of medication, approved claim, target species, directions for use, warning, cautions) to ensure effective and safe use by the users of the medicated feed.

6. Implement appropriate production practices to prevent contamination of unmedicated *feed* such as good manufacturing practices to avoid carry over and cross contamination from medicated *feed*.

Article 6.2.~~8.~~11.

Responsibilities of aquatic animal producers

Aquatic animal producers should implement health programmes on their *aquaculture establishments* in order to promote *aquatic animal* health, welfare and food safety, as well as environmental sustainability. ~~This can be done through adequate planning of culture strategies to maintain *aquatic animal* health through *biosecurity* programmes, husbandry, nutrition, vaccination, maintenance of good water quality, etc.~~

Aquatic animal producers are responsible for implementing *aquatic animal* health and welfare programmes, including good husbandry practices and *biosecurity plans* in *aquaculture establishments* (in accordance with Chapter 4.1) to reduce the need for the use of *antimicrobial agent*s in *aquatic animal*s, and to promote aquatic animal health and food safety.

Aquatic animal producers should use *antimicrobial agent*s only on the prescription or equivalent of a *veterinarian* or other *aquatic animal health professional* authorised to prescribe veterinary medicines, and follow directions on the dosage, method of application, and withdrawal period.

Aquatic animal producers should ensure that *antimicrobial agent*s are properly stored, handled, and disposed.

Aquatic animal producers should keep adequate records of *antimicrobial agent*s used, bacteriological and susceptibility tests, and make such records available to the *veterinarian* or ~~other~~ authorised *aquatic animal health professional*.

Aquatic animal producers should inform the *veterinarian* or other *aquatic animal health professional* of recurrent *disease* problems and lack of efficacy of *antimicrobial agent* treatment regimes.

Article 6.2.12.

Responsibilities of owners and keepers of aquatic animals for purposes other than human consumption

Aquatic animal owners and keepers of *aquatic animals* for purposes other than human consumption, (e.g. for ornamental, research, bait, and stock enhancement uses; and sea lice 'cleaner' fish) guided by a *veterinarian* or authorised *aquatic animal health professional*, have a responsibility to implement *aquatic animal* health and welfare programs, including *biosecurity*, to reduce the need to use *antimicrobial agents* to promote the health and well-being of *aquatic animals*.

Article 6.2.~~9.~~13.

Training of users of *antimicrobial agents*

~~The training of users of *antimicrobial agents* should involve all the relevant organisations, such as relevant regulatory authorities, pharmaceutical industry, veterinary schools, research institutes, and veterinary professional organisations and other approved users such as *aquatic animal* owners.~~

Training related to the use of *antimicrobial agent*s in *aquatic animals* is a shared responsibility of all stakeholders. The training may include:

a. the ability of *antimicrobial agent*s to select for resistant microorganisms in *aquatic animals* and the aquatic environment and the importance of that resistance to public health and animal health and the relevant animal environment;

b. the need to observe responsible and prudent use principles for the use of *antimicrobial agent*s in *aquatic animals* in agreement with the provisions of the regulatory approval, national and international guidelines and recommendations from the WOAH List of *Antimicrobial Agent*s of Veterinary Importance;

c. information on the appropriate storage conditions before and during use and proper administration at the farm level, as well as disposal of unused or expired veterinary medicinal products;

d. training in existing and new methodologies for pathogen identification, susceptibility testing, molecular detection of resistance and *risk assessment* models;

e. interpretation of relevant *risk assessment* outputs for antimicrobial resistance derived from the use of *antimicrobial agent*s in *aquatic animals* and how to use these outputs to inform the development of *risk management* and *risk communication* strategies;

f. the collection and reporting of antimicrobial resistance and antimicrobial use data to the *Competent Authority* to complement existing national and international monitoring programmes;

g. information on *disease* prevention, management and *biosecurity* mitigation strategies that can contribute to reducing the need to use *antimicrobial agent*s in *aquatic animal*s.

Article 6.2.~~10.~~14.

Knowledge gaps and ~~R~~research

Relevant regulatory authorities and other stakeholders should encourage public- and private-funded research, and public-private partnerships in a One Health approach ~~T~~to address ~~the significant lack~~ knowledge gaps ~~of information~~ for numerous species of *aquatic animals* including~~, the relevant regulatory authorities and other stakeholders should encourage public- and private-funded research~~, the following areas:

a. improve the knowledge about the mechanisms of action, pharmacokinetics and pharmacodynamics of *antimicrobial agents* to optimize the dosage regimens for veterinary medical use and their effectiveness;

b. improve the knowledge about the mechanisms of selection, co-selection, emergence and transmission of resistance determinants and resistant microorganisms in *aquatic animal* populations, and between *aquatic animals*, humans and the relevant *aquatic animal* production environment, including along the food chain;

c. develop practical models for applying the concept of *risk analysis* to assess the animal and public health concerns linked to the development of antimicrobial resistance in *aquatic animals* and *aquatic animal*-derived foods;

d. further develop protocols to predict, during the regulatory approval process, the impact of the

proposed use of the *antimicrobial agents* in *aquatic animals* on the rate and extent of antimicrobial resistance development and spread to animals, humans, plants and the environment, following a One Health approach;

e. assess the primary drivers leading to use of *antimicrobial agents* in *aquatic animals*, and the effectiveness of different interventions to change behaviour and reduce the need to use *antimicrobial agents* in *aquatic animals;*

f. develop safe and effective alternatives to the use of *antimicrobial agents*, new *antimicrobial agents*, rapid diagnostics, and vaccines for infectious *diseases* to reduce the need for antimicrobial use in a*quatic animals;*

g. improve knowledge on the role of the environment on the persistence of antimicrobial agents, and the emergence, transfer and persistence of antimicrobial resistance determinants and resistant microorganisms in the relevant *aquatic animal* production environment.