Food and Agriculture Organization of the United Nations

METHODOLOGY TO ANALYSE AMR-RELEVANT LEGISLATION IN THE FOOD AND AGRICULTURE SECTOR

GUIDANCE DOCUMENT FOR REGULATORS

DRAFT FOR PUBLIC REVIEW

METHODOLOGY TO ANALYSE AMR-RELEVANT LEGISLATION IN THE FOOD AND AGRICULTURE SECTOR

GUIDANCE DOCUMENT FOR REGULATORS

DRAFT FOR PUBLIC REVIEW

Food and Agriculture Organization of the United Nations

Rome, 2020

Table of Contents

Acknowledgements

This document was prepared by Yingjing (Sara) Li, Carmen Bullón Caro and Ambra Gobena, from the Development Law Service (LEGN) of the Food and Agriculture Organization of the United Nations (FAO), with the financial support of the Fleming Fund of the UK.

It has benefitted from the technical expertise of the former and current members of the FAO Antimicrobial Resistance Working Group (AMR-WG), who have provided guidance, input, and feedback during various stages of its development, particularly including Anoek Backx, Daniela Battaglia, Sarah Cahill, Katinka De Balogh, Alejandro Dorado García, Suzanne Eckford, Gunilla Ecklund, Emmanuel Kabali, Irina Kireeva, Eva Kohlschmid, Francesca Latronico, Jeffrey Lejeune, Juan Lubroth, Beatrice Mouille, Hendrick Jan Ormel, Alessandro Patriarchi, Saskia Reppin and Antonio Valcarcel. Other contributors include Marcelo Campbell, Sophie Decock, Romina Faragasso, Valerie Johnson and Teemu Viinikainen.

The authors wish to gratefully acknowledge the input from David Sherman, Coordinator of the OIE Veterinary Legislation Support Programme (VLSP) and Camille Loi, VLSP Legislation Programme Officer, from the World Organisation for Animal Health (OIE).

Disclaimer

This document was prepared as basis for the field work of FAO, and to support the work of the national legal consultants working on AMR projects including a legislative component. It can serve lawyers and regulators to identify and better understand the connection between law and AMR. Its format and content are adapted to its intended purpose. At the time of this publication, this document is still in its draft form, and subject to change based on further feedback. Feedback and input on this document is most welcome. You can send your comments and suggestions to Carmen.Bullon@fao.org.

The views expressed in this information product are those of the author(s) and do not necessarily reflect the views or policies of FAO.

FAO is not responsible for any use or interpretation of this document that is not under the direct supervision of the FAO Development Law Service.

Data protection

By participating to this public consultation, you agree that personal data shared with FAO will be processed by FAO and/or its partners, authorized vendors or subcontractors for the purpose of this review process, and in accordance with FAO's rules, policies and practice, to the exclusion of any single national system of law. For any information, please contact LEGN-Chief@fao.org.

LIST OF ABBREVIATIONS

ADI	Acceptable Daily Intake
AM	Antimicrobial
AMR	Antimicrobial Resistance
AMU	Antimicrobial Use
CAC	Codex Alimentarius Commission
CIAs	Critically Important Antimicrobials
FAO	Food and Agriculture Organization of the United Nations
GHP	Good Husbandry Practices
GPP	Good Production Practices
IPPC	International Plant Protection Convention
MRLs	Maximum Residue Limits
NAPs	National Action Plans
NPPO	National Plant Protection Organization
OIE	World Organisation for Animal Health
UNGA	United Nations General Assembly
VMPs	Veterinary Medicinal Products
WHO	World Health Organization
WTO	World Trade Organization

I. Context and background information

What is AMR?

Antimicrobial resistance (AMR) refers to microorganisms – bacteria, fungi, viruses, and parasites – that have acquired resistance to antimicrobial (AM) substances (FAO, 2016). The Codex Alimentarius defines AMR as "*the ability of a microorganism to multiply or persist in the presence of an increased level of an antimicrobial agent relative to the susceptible counterpart of the same species*" (Codex Alimentarius Commission, 2011, p. 4). An AM agent, in turn, is defined as "*any substance of natural, semi-synthetic, or synthetic origin that at in vivo concentrations kills or inhibits the growth of microorganisms by interacting with a specific target*" (Codex Alimentarius Commission, 2011, p. 4). Accordingly, AM is the overarching name for antibiotics (that work against bacteria), antivirals (against viruses), anti-fungals (against fungi), and anti-parasitics (against parasites). For example, in the plant health context, AMs are utilized against certain plant pests.

While the phenomenon of AMR can occur naturally through microbial adaptation to their surrounding environment, it has been exacerbated by inappropriate and excessive use of AMs. Through the use, overuse, and misuse of AMs, especially in the human health and the agriculture[1] sectors, more and more microorganisms have become (or are becoming) resistant to the drugs to which they were previously susceptible. Resistance to AMs used in human and agriculture sectors is determined by the same mechanisms, and this is of extreme importance if we consider that, with a few exceptions, the same AM classes[2] are used in human and veterinary medicinal products. This is threatening the efficacy of AMs available for treatable infections and diseases, including those considered critically important for human health, and which are used as the last resort in the most serious and difficult cases. This is a global "One Health" concern that affects not only plant and animal health, but more generally public health and the environment, requiring a holistic and multi-sectoral approach to best address the issue.

A range of factors have contributed to AMR, such as: i) massive non-therapeutic use of AMs ; ii) poor therapy adherence, incorrect application, wrong dosage or use for unregistered purposes/off-label uses; iii) over-the-counter or internet sales; iv) availability of falsified, substandard or poor quality AMs; v) the lack of regulation, poor legal implementation and oversight of use of AMs; or vi) failure to comply with good manufacturing or production practices for AMs, among others. The consequences of AMR include the failure to successfully treat infections, leading to more severe or prolonged illness, death, production losses and negative consequences for livelihoods and food security (FAO, 2016). The health consequences and economic costs of AMR are estimated at 10 million annual human fatalities and a 2 to 3.5 percent decrease in global Gross Domestic Product, or 100 trillion USD by 2050 (O'Neill, 2014), although the real consequences of AMR remain unpredictable (Smith and Coast, 2013).

AMR has become a global health threat that requires worldwide and multi-sectoral action to curb it. In response, global action has been initiated to curb the development of AMR. In the lead-up to the UN General Assembly (UNGA) and its Declaration in September 2016 (UNGA, 2016), the three organisations dedicated to human, agricultural and animal health (the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health

[1] FAO adopts a very broad concept of "agriculture" which includes (among other areas) animal health, plant health and food safety, as well as the protection of the environment from risks resulting from agricultural activities

[2] The Codex Alimentarius defines an AM class as "antimicrobial agents with related molecular structures, often with a similar mode of action because of interaction with a similar target and thus subject to similar mechanism of resistance. Variations in the properties of antimicrobial agents within a class often arise as a result of the presence of different molecular substitutions, which confer various intrinsic activities or various patterns of pharmacokinetic and pharmacodynamic properties." Codex Alimentarius. Definitions, Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance, CAC/GL 77- 2011. p. 4. Retrieved from http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B77-2011%252FCXG_077e.pdf.

(OIE)), were tasked to assist countries with developing their national action plans (NAPs) on AMR by May 2017. A crucial aspect of such NAPs would be appropriate and workable legal frameworks that support the policy objectives to contain the development and spread of AMR.

Global initiatives on AMR

WHO, FAO and OIE (the Tripartite organisations) have joined forces to advocate for the need to tackle AMR in all sectors. The Tripartite developed a Global Action Plan on AMR that invites countries to establish National Action Plans on AMR (NAPs). NAPs can address areas that are cross-cutting or focus on specific, relevant sectors, depending on the individual country's needs, but should ensure consistency and compliance with existing guidance and international standards (see below on international standards). NAPs should be aligned with the Global Action Plan and the FAO Action Plan on AMR.

In the food and agriculture sectors, the FAO Action Plan on AMR focuses on four areas of action: improved awareness, surveillance and monitoring (evidence), governance, and good practices (FAO, 2016). These four focus areas support the Global Action Plan's objectives of: 1) improving awareness and understanding of AMR through communication, education and training; 2) strengthening the knowledge and evidence base through surveillance and research; 3) reducing the incidence of infection through effective sanitation, hygiene and infection prevention measures; 4) optimizing the use of AM medicines in human and animal health, and; 5) developing the economic case for sustainable investment that takes account of the needs of all countries, and increases investment in new medicines, diagnostic tools, vaccines and other interventions (WHO, 2015).

In addition, WHO and OIE promote various initiatives to prevent the overuse of critically important AMs, as well as to restrict their use in animals, which are key elements for the preservation of the benefits of AMs. WHO publishes a list of Critically Important AMs for Human Medicine, which classifies and ranks medically important AMs according to criteria such as their importance for human treatments, availability of alternatives, cross-resistance selection and frequency of use (WHO, 2017a). This ranking facilitates focusing management efforts, such as restrictions on usage or bans for animal use of critically important medicine for humans (e.g. fluoroquinolones, macrolides and 3rd-4th generation cephalosporins). WHO also publishes the WHO Model List of Essential Medicines, which includes categorizations of various antibiotics into the groups of Access, Watch, and Reserve antibiotics (WHO, 2017b). In the area of veterinary medicine, the OIE has developed the List of AM Agents of Veterinary Importance, categorizing AM agents used in food-producing animals as Veterinary Critically Important AMs, Veterinary Highly Important AMs and Veterinary Important AMs (OIE, 2019a).

Legislation as an effective tool in the fight against AMR

Legislation forms an essential part of the governance structure in aspects relevant for AMR, playing a vital role in addressing the abuse, overuse, misuse and release into the environment of AMs and resistant microorganisms, which will greatly contribute to minimizing the development and spread of AMR. Legislation also form the backbone for appropriate frameworks to prevent the introduction and spread of pests and diseases in countries, contributing towards minimizing the need to use AMs. Legislation could contain the key regulatory controls within a sector, establish linkages among the various sectors and activities in the different areas with an impact on AMR, and facilitate coordinated implementation by the different authorities - all contributing to a more comprehensive regulatory prevention and response to the threat of AMR.

At the national level, there have been different legal initiatives in some countries to combat AMR in the forms of controlling the ways AMs are manufactured, distributed and disposed; the way AMs are used; and provisions for the prevention, surveillance and control of pests and diseases.

Most countries have laws or regulations addressing some aspect of AM control. Such legislation is only one part of the broad spectrum of regulatory areas with implications in AMR. Legislation on AMs should cover all stages of the lifecycle of the AM substances - from authorisation and registration of AMs, and the manufacture, distribution (sale, import, export etc), use and disposal of such products.

Each of the various stages outlined above entails a range of institutional and legal implications.

For example, regarding the use of AMs, one of the recommendations made in the UK Swann Report in 1969 (published in 1969 and served as the basis for regulatory decisions to follow in the UK and the EU) was the prohibition of antibiotics used in human medicine to be used as growth promoters in the livestock sectors (Swann et al., 1969). The Swann report also recommended the setting up of a committee with authority to review and recommend antibiotic use in humans, animals and horticulture (Soulsby, 2007). Since its publication, several countries have taken various forms of regulatory action to fight AMR and, in light of this, a number of relevant regulatory measures have been identified. Sweden, for instance, introduced legislation to ban the use of AM as growth promoters (AGPs) in 1986. All AMs for use in animals have since then been classified as veterinary medicinal products[3] (VMPs), with their use in animals becoming restricted to use only when prescribed by veterinarians. In the European Union, the Feed Additives Regulation 1831/2003/EC introduced a total ban on antibiotics as growth promoters from 1 January 2006. In the last decade, the U.S. Food and Drug Administration (FDA) has also taken various steps to curb the development and spread of AMR, leading up to eliminating the use of medically important antibiotics for production purposes.[4] Further to the prohibition in the use of AMs for growth promotion, the regulatory focus of some European countries regarding use has evolved to:

- Limiting the veterinary use of critically important AMs (CIAs) to only situations when they are the last resort. In some countries, certain CIAs (e.g. 3rd, 4th and 5th generation cephalosporins, fluoroquinolones, macrolides, colistin) have been limited to only culture-proven infections, or they have included special taxation of these drugs.
- Establishing mechanisms for monitoring AM use (AMU) and AMU benchmarking systems for farmers and veterinarians to reduce the overall use of AMs in food production (e.g. yellow card in Denmark, mandatory targets in the Netherlands).

With regard to disposal on the other hand, legislation should also pay attention to the effects of AM residues introduced into the environment and the contamination of the environment, the soil and water resources with AMs, AMR microorganisms or resistant genes. This is important not only for environmental protection purposes, but also to prevent the human consumption of contaminated food or water, or the use of agricultural inputs potentially contaminated with AMR microorganisms or residues. Current water and wastewater treatment technologies are not adequate to remove all AM compounds, and hence AMR microorganisms are found to be developing and spreading in multiple aquatic habitats downstream of cities, agriculture and aquaculture activities. Regulatory control over environmental pollution, including the regulatory mechanisms to control pollutant activities, could also help identify tools that can be used to contribute towards efforts in climate change mitigation and

[3] The OIE defines "Veterinary Medicinal Product" as "any product with approved claims to having a prophylactic, therapeutic or diagnostic effect or to alter physiological functions when administered or applied to an animal". Retrieved from http://www.oie.int/en/standard-setting/terrestrial-code/access-online/?htmfile=glossaire.htm

[4] See, for example: FDA Final Rule: Veterinary Feed Directive, 2015, https://www.federalregister.gov/documents/2015/06/03/2015-13393/veterinary-feed-directive; FDA Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, 2012, https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf; FDA Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209, 2013 https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf; Timeline of FDA Action on Antimicrobial Resistance, https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm438426.htm.

adaptation strategies. This would involve not only laws narrowly focusing on AMs but possibly broader environmental or agricultural legislation as well.

An appropriate institutional and regulatory framework would also be required more broadly for the prevention, surveillance and control of pests and diseases. Appropriate plant health, animal health, pesticides or fisheries and aquaculture legislation can serve as basis for the introduction of the necessary regulatory control mechanisms (licenses, permits), good production practices and biosecurity measures that would help to improve the sanitary and phytosanitary status and reduce the need for AMs in the first place. By improving the overall regulatory structure of agricultural systems, agriculture production and agriculture health would also be strengthened, contributing to nutritious and safe food production and food security and to promoting the human rights to food and safe water.

Having a broad perspective of the legal frameworks required to address AMR as outlined above not only results in a reduction in the occurrence of AMR, but also aims at improving the human, animal, and environmental health of the country, promoting the right to health and the right of people to a healthy environment. Regulators have traditionally concentrated on selected areas and activities with regarding to ways to reduce AMR. This has resulted in an often well-developed national legislation on the regulatory frameworks for AM, while insufficient attention has been given to other aspects, such as the release of AM into the environment or the use of contaminated agricultural inputs. Similarly, food safety regulatory control is normally effective in monitoring the Maximum Residue Limits (MRLs) of AM in food, as well as for setting the microbiological criteria applicable to food control, but in this exercise, countries have not paid attention to the potential resistance *of the microorganisms* transmitted through food. Finally, the level of awareness and regulatory control in the use of AMs for crop production might not be similar to the situation in the veterinary domain, resulting in less regulatory consideration of AMR factors in crop-related legislation vis-à-vis the veterinary domain. As a consequence, while many countries have introduced AMR considerations into their veterinary legislation (including terrestrial and aquatic animals), this is rarely the case in other areas of concern, such as plant production and protection, environmental protection or water quality.

It should also be highlighted that the dynamic nature of the scientific research in this area makes it difficult to introduce effective regulatory control and monitoring mechanisms.

Thus, the working premise of this guidance document is that mechanisms to control and reduce AMR are found in a variety of different legal instruments at the national level. Such instruments were not typically developed to directly address AMR and might not include specific references to AMR. Nonetheless, legislative frameworks for animal health, VMPs, plant health, pesticides, environment, food safety, etc. may include the necessary regulatory powers as well as mechanisms (prohibitions, licenses, permits) to effectively address AMR. With this in mind, the identification of the relevant regulatory areas and related legal issues become essential to assess and strengthen the capacity of a national legal framework to prevent and address AMR.

International reference standards

Before exploring the range of regulatory areas at the national level, it is useful to canvass the key international reference texts related to animal health, plant health and food safety that offer guidance on various elements of AMR-relevant legislation. These standards are recognised by the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). Beyond these core international standards, a range of other guidance exists relating to water quality, wastewater discharge, aquaculture production and other regulatory topics impacting AMR.

As the relevant standard-setting organization for the WTO SPS Agreement concerning animal health and zoonoses, the OIE has also developed standards relating to animal health, animal welfare, and animal production (OIE, 2020), and specifically on (VMPs) as well as AMR. The Terrestrial Animal Health

Code (Terrestrial Code) and Aquatic Animal Health Code (Aquatic Code) cover animal health, from the farm level through to primary processing. Chapter 3.4 on veterinary legislation offers specific guidance on animal diseases (article 3.4.9), and veterinary medicines and biological (Article 3.4.11). Section 6 of the Terrestrial Code governs on Veterinary Public Health, and contains veterinary public health, and contains several chapters on AMR.[5] In the Aquatic Code, Section 6 also includes different chapters that specifically address AMU in aquatic animals.

The standards, guidelines and codes of practice are developed by the Codex Alimentarius Commission (CAC) are the international reference standards for food safety, spanning from primary production to consumption and for the purposes of the safety, quality and fairness of international food trade. CAC has been developing texts that specifically address the issue of foodborne AMR since 2005.[6] In 2015, CAC compiled the *Guidelines for risk analysis of foodborne AM resistance (CAC/GL 77-2011)* and the *Code of practice to minimize and contain AM resistance (CAC/RCP 61-2005)* into one publication of Codex texts on foodborne AMR in support of the Global Action Plan (FAO and WHO, 2015a). Since 2017, the Task Force on Antimicrobial Resistance has been re-established with the objective to develop science-based guidance on the management of foodborne AM resistance (Codex Alimentarius Commission, 2017). In addition, the CAC approves reference MRLs for veterinary drugs (Codex Alimentarius Commission, 2020a) and pesticides (Codex Alimentarius Commission, 2020b).

The IPPC international standards for phytosanitary measures are developed to support contracting parties to strengthen their phytosanitary systems to prevent the introduction and spread of pests, including through measures that would minimize the impact of pests on environment and plant health.

II. Scope and approach of Guide

This document aims to support and assist national regulators in the identification and analysis of existing legislation relevant to AMR in a national legal system. Such approach should begin by taking as basis international reference standards and good practices. This guide focuses only on the agricultural sector, understanding agriculture as all activities related to terrestrial and aquatic animal production and health, plant production and health, forestry production and environmental protection in the agricultural sector (including environment, related wastes and water). Legal and regulatory aspects relating directly to human health are excluded from the scope of this guidance.

This document highlights a non-exhaustive list of regulatory areas with an impact on AMR. For each regulatory area, its linkage to AMR is explained, followed by the key elements to be aware of during a legal analysis.

It should be emphasised at the outset, that this guidance document is useful to identify legal weaknesses across a range of sectors relevant to addressing AMR. It is not, per se, sufficient to recommend or serve as basis for legal reform. For this purpose, countries should evaluate the impact of each of these regulatory weaknesses on the implementation of their AMR National Action plan and policy priorities, or in other words, which legal reforms would give more direct and effective results to monitor and control AMR.

It should be noted that in this guidance document's focus on preventing the need for AMs, the premise is that robust animal health, plant health and food safety legislation reduces the incidence of pest and

[5] Namely Chapter 6.7. Introduction to the recommendations for controlling antimicrobial resistance; 6.8: Harmonisation of national antimicrobial resistance surveillance and monitoring programmes; 6.9 Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals; 6.10 Responsible and prudent use of antimicrobial agents in veterinary medicine; and 6.11 Risk analysis for antimicrobial resistance arising from the use of antimicrobial agents in animals.
[6] See Codex Alimentarius. 2005. Codex texts on foodborne antimicrobial resistance: Guidelines for risk analysis of food borne antimicrobial resistance (CAC/GL 77-2011), 2011; Code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005), 2005. These texts are currently undergoing revision. Also, there is a new Guideline on AMR surveillance under development.

disease incursions and outbreaks and the thus minimizes the need for AMs. Such broader regulatory frameworks are not analysed in an exhaustive manner, rather the focus is on the key elements that would have a clear impact on disease containment and AMU. Following an identification of the relevant legal instruments that govern each of the regulatory areas, regulators may consult the specific questions provided in this document to analyse the provisions and elements specific to AMR. It is possible that a legal instrument governs more than one of the legal areas identified, and in this case, different provisions of the same law will have to be used for different sections.

It is necessary to determine whether the institution responsible for implementing the law under analysis has been given the legal mandate and authority necessary to develop or approve implementing legislation that provides an opportunity or leeway to address specific needs. Given the breadth of legal areas and multitude of responsible institutions, it would also be important to identify any existing coordination mechanisms (see Chapter III, section 9 of this document).

Whenever reference is made to "legislation", this term shall be understood to include primary and secondary legislation such as, for example, laws, acts, regulations, ordinances and decrees. Some key elements listed in this guide may be found in national standards which, depending on the national legal system, may or may not be considered as part of its legislation. This might be the case, for instance, with quality standards for feed or VMPs. In such a scenario, it is important to ascertain whether: (i) the standard is binding; (ii) if so, under which law; and (iii) the competent authorities for its approval and update; and (iv) the authority(ies) responsible for monitoring implementation, control and enforcement. Finally, in many instances, the questions in this document will focus on regulatory mechanisms that could potentially be used by the competent authority to introduce AMR and AMU considerations, rather than on the existence of such AM-specific aspects in the body of the legislation. For instance, a water law that gives the competent authority capacity to approve, monitor and control quality requirements, will be sufficient for such government to introduce AMR-related considerations in water management. In this sense, the document does not include specific references to AMR criteria in every area. Instead, it focuses on the key regulatory mechanisms a country can use to address AMR and AMU.

In Chapter III, focus is given first to veterinary legislation. Special attention is paid to the regulatory framework for VMPs, taking into consideration their whole life cycle (from production through ultimate disposal). Next, consideration is given to the role of prevention, and the potential animal health and production practices that may have a role in reducing the need for AMs, including animal welfare, good production and handling practices, hygiene measures and occupational health and safety at work for farmers and other operators. Finally, feed legislation brings a number of elements relevant in the fight against AMR, particularly the production and use of feed medicated with AMs.

Next, pesticides legislation is analysed with the understanding that a number of pesticides are also AMs used for human and livestock purposes and, in this sense, may create resistance to AMs used for human and animal health. Furthermore, the use of pesticides may result in resistance of plant pests, with consequences on agricultural production, food security, environmental protection and economic development. For the same reason, the prevention of plant diseases (as a way to reducing the need for AMs) is addressed, as this can serve to improve plant health and minimize the need for antimicrobials.

The sections that follow examine, respectively, the legislation aimed at monitoring, controlling and/or minimizing the impact of AMs into food products and food production systems, the broader environment, soil and waste as well as on water resources.

Chapter III also addresses the regulatory instruments countries may put in place to ensure institutional coordination among AMR stakeholders, including national authorities at the central and decentralized levels.

In Chapter III, every area includes an explanation of why the area is relevant for AMR, as well as a description of the elements relevant for AMR. This is followed by a number of questions that highlight the key regulatory issues that need to be taken into consideration in the analysis of the legislation.

III. Legal areas relevant for AMR

1) Veterinary medicinal products

a. Background

One of the most important regulatory areas for curbing the development and spread of AMR in food and agriculture is the regulation of VMPs. All the elements of the regulatory framework for VMPs may have an impact on AMR and AMU (whereas other sectors discussed below may only have some elements that have an AMR impact). Thus, the totality of elements for a regulatory framework for VMPs must be examined comprehensively, with a focus on those aspects of special importance for AMR.

To provide a complete basis for action, regulation in this area should cover all stages of the lifecycle of veterinary medicinal products, including: authorization/registration, production/manufacturing, import, export, distribution, sale, and disposal (although the latter may not frequently be found in VMP legislation specifically). Inadequacies in the regulation of any stage along the chain could contribute to the increase in development and spread of AMR.

b. Key elements of VMP legislation

Countries may choose to regulate VMPs in various legal instruments (see below point c.1. "*where can this be regulated*"). This section provides a non-exhaustive list of the most relevant elements of legislation on VMPs, with a focus on those of special importance for AMR.

The OIE Terrestrial Code Article 3.4.11, Chapter 6.8 and Article 6.10.3, the OIE Terrestrial Manual Chapter 3.4., as well as the Codex Alimentarius Code of Practice to Minimize and Contain Antimicrobial Resistance[7] form the basis of the elements highlighted in this section.

It is important that VMP legislation ensures coordination in the authorization and management of all VMPs, including AMs for terrestrial and aquatic animals, as well as other medicinal products such as vaccines or biologicals. Similar guarantees in terms of quality and control that apply to human medicines should be applicable to the medicines administered to terrestrial and aquatic animals, as otherwise the risk is that low quality medicinal products arrive to the wrong species.

VMPs legislation should provide definitions of key terms, such as "Veterinary Medicinal Product". These definitions are the essential basis for the smooth implementation of legislation on VMPs and should be consistent with those provided by the international standards.[8]

[7] For a detailed list of the responsibilities of the regulatory authorities, see Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005), pages 4 to 9. See also Codex Texts on foodborne antimicrobial resistance http://www.fao.org/3/a-i4296t.pdf.

[8] See page 15 of the Codex Code of Practice to Minimize and Contain Antimicrobial Resistance, and the glossaries of the OIE Terrestrial Code and Manual http://www.oie.int/index.php?id=169&L=0&htmfile=glossaire.htm.

The identification of the competent authority[9] and the recognition of its functions, powers and mandate is one of the most important elements of VMP legislation. According to Articles 3.4.11 and 6.10.3 of the OIE Terrestrial Code, as well as the sections 9 to 16 of the Codex Code of Practice to Minimize and Contain Antimicrobial Resistance, the competent authority should have the powers to:

(i) regulate the authorization of VMPs, including labelling, packaging and surveillance to monitor compliance;

(ii) grant marketing/manufacture authorization to VMP producers, importers or distributors;

(iii) develop and approve quality standards for VMPs and monitor compliance;

(iv) provide veterinarians with the appropriate information through product labelling and other means, in support of prudent use;

(v) develop up-to-date guidelines on data requirements for evaluation of AM application;

(vi) approve national strategies to promote prudent use of AM, implement Good Production/Husbandry Practices as well as preventive measures, such as vaccination campaigns/policies;

(vii) actively combat the manufacture, advertisement, trade, distribution and use of illegal and counterfeit (substandard and falsified) active pharmaceutical ingredients and products;

(viii) regulate, monitor and control the use of VMPs, with special focus on AM, and critically important AMs (WHO, 2017a) or AM of veterinary importance (OIE, 2019a);

(ix) regulate and authorize the production/manufacturing, storage, sale and distribution (including import and export) of VMPs, as well as and VMPs traceability and recall;

(x) regulate the use of AM and other VMPs, paying attention to the prohibition or restriction of specified uses, the requirement for prescription and provision of AM to end users;

(xi) restrict certain activities (such as prescription, administration or sale) to be only conducted by authorized qualified professionals;

(xii) regulate, monitor and control the sale, advertisement, and claims of VMPs;

(xiii) register and authorize VMP operators;

(xiv) develop and establish effective pharmacovigilance, surveillance and enforcement systems to ensure the implementation of the legislation;

(xv) encourage public- and industry-funded research, including research on the ecology of AMR.

Authorization

Legislation should delineate the criteria and procedures for VMPs authorization and define its elements (application for registration, coordination with other entities, decision making, publication, etc.). As per the OIE Terrestrial Code, Article 6.10.3, the authorization of AMs used for human purposes and for veterinary purposes should be coordinated. In defining procedures, legislation should also establish rules providing for transparency in decision making. More specifically, the procedure for authorization

[9] For a detailed list of the responsibilities of the regulatory authorities, see Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005), pages 4 to 9. In Codex Texts on foodborne antimicrobial resistance http://www.fao.org/3/a-i4296t.pdf.

should guarantee that decisions are free from any commercial, financial, hierarchical, political or other pressures.

As with other input-related legislation, legislation on VMPs frequently includes a clear prohibition to put into the market any product that is not registered as prescribed, with certain exceptions for emergencies and research. This type of prohibition has a very strong impact on the market and should be accompanied by appropriate monitoring and enforcement mechanisms.

According to Chapter 3.4 of the OIE Terrestrial Code, veterinary legislation should ensure that only authorized veterinary medicinal products are placed on the market, with special provisions for medicated feed, and products prepared by authorized veterinarians or pharmacists. Legislation should also address "the technical, administrative and financial conditions associated with the granting, renewal, refusal and withdrawal of authorizations".

Following the section 9 to 16 of the Codex Code of Practice to Minimize and Contain AMR, the authorization process should include the following elements:

(i) regulate the authorization of VMP and, to this purpose, establish and implement efficient statutory registration procedures that evaluate the quality, safety and efficacy of VMP;

(ii) request from pharmaceutical companies the data necessary for granting marketing authorization and, for this purpose:

a. assess the risks to both animal and humans resulting from the use of AM in food producing animals (safety evaluation), taking into consideration

i. each individual AM as well as the class of AM to which the active principle belongs;[10]

ii. the potential impact of the proposed use in food producing animals on human health;

iii. when possible, an assessment of the potential of the VMP or its ingredients, to select for resistance;

b. approved product labelling, particularly its dose ranges or different durations of treatment are indicated, including the conditions that will minimize the development of resistance (if available);

c. establish the species for which the product is authorized; the authorized route of administration (topical, sub-cutaneous, intravenous, intramuscular injection, in feed or water), the acceptable daily intake (ADI), MRLs and withdrawal periods,[11] as well as storage requirements.[12]

d. Grant marketing authorization on the basis of the data submitted by the pharmaceutical industry or applicant and only if the criteria of safety, quality and efficacy are met (OIE, 2019b, Article 6.10.3, para. 1).

[10] Regarding this, OIE Terrestrial Code, Chapter 6.10, Article 6.10.3, para. 1 clarifies that "The evaluation should focus on each individual antimicrobial agent and the findings should not be generalised to the antimicrobial class to which the particular active ingredient belongs".

[11] Period between the treatment and the slaughter of the animal to minimize residues of antimicrobials. Codex Alimentarius. Glossary of Terms and Definitions (Residues of Veterinary Drugs in Food), CAC/MISC 5-1993. Withdrawal Time and Withholding Time: This is the period of time between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the maximum residue limit for this veterinary drug (MRLVD).

[12] OIE Terrestrial Code, Chapter 6.10, Article 6.10.3, para. 5 includes criteria for the establishment of ADI, MRL and withdrawal periods in food producing animals.

e. Within the framework above, if new VMPs are necessary for specific needs related to the treatment of animal diseases, expedite the authorization processes.

(iii) Countries without the resources to implement an authorization procedure and whose supply of VMPs mostly depend on imports from foreign countries,[13] should:

a. ensure the efficacy of administrative controls on importation of VMPs;

b. seek and validate information on the status of authorizations valid in other countries;

c. develop technical cooperation with experienced authorities to check the quality of imported VMPs as well as the validity of the recommended conditions of use.

Labelling

As part of the authorization process, legislation should give a basis for the government to approve and monitor the information displayed on product labels. Labels should be written in a language that is understandable for users (local/official language). It should also include a summary of product characteristics containing the necessary information for the appropriate use of VMPs.[14] This summary should contain the following information:

- Active ingredient and class;
- Pharmacological properties and any potential adverse effect;
- Target animal species and, as appropriate, age or production category;
- Therapeutic indications;
- Target microorganisms;
- Dosage regimen and administration route;
- Withdrawal periods;
- Incompatibilities and interactions;
- Storage conditions and shelf-life;
- Instructions for operator safety;
- Particular precautions before use;
- Instructions and particular precautions for the return or proper disposal of un-used or out-of-date products;
- Information on conditions of use relevant to the potential for selection of resistance should be included, for the purpose of guidance on prudent use;
- Contraindications.

Similarly, it is important that legislation grants the concerned authority the power to regulate VMP packaging, because packages and packaging materials may have a direct impact on the product efficacy and safety and a regulatory promotion of, for instance, packages that include the standard needed dosage, could help preventing leftovers, obsolete stocks and disposal into the environment. Claims included into VMPs packages should be minimum, focus on medical purpose and use instructions and avoid providing misleading information to the user.

[13] See OIE Terrestrial Code, Chapter 6.10, Article 6.10.3, para. 1 and Codex Code of Practice, Section 3.1.

[14] See Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005), Sections 9-16. See also OIE Terrestrial Code, Chapter 6.10, Article 6.10.3, para. 7.

Quality control

Legislation should provide a legal basis to regulate the quality control of VMPs, before and after authorization. This should include the quality of their raw materials, safety and efficacy testing, clinical and non-clinical trials, quality standard setting, quality monitoring, and post-marketing pharmacovigilance surveillance in the form of both general epidemiological surveillance, and specific surveillance for the impact of the use of specific AM agents.[15]

More specifically, Chapter 3.4 of the OIE Terrestrial Code clarifies that veterinary legislation should address the following elements:

a. The conduct of clinical and non-clinical trials to verify all claims made by the manufacturer;
b. Conditions for the conduct of trials;
c. Qualifications of experts involved in trials;
d. Surveillance for adverse effects arising from the use of VMPs.

Under the legal basis to regulate the quality control of VMPs, the Codex Code of Practice to Minimize and Contain AMR and Chapter 6.10 of the OIE Terrestrial Code highlight the following elements for VMP quality control regulation. These should:

a. be based on good manufacturing practices;
b. ensure that the quality and concentration (stability) in the marketed dosage form is maintained and properly stored up to the expiry date established under the recommended storage conditions;
c. ensure the stability of VMPs when they are mixed with feed or drinking water;
d. ensure that the AM agents and the VMPs containing them are manufactured to the appropriate quality and purity to guarantee their safety and efficacy;
e. verify that the analysis specifications of AM agents used as active ingredients for VMPs comply with the registration documentation requirements.

The Codex Code of Practice to Minimize and Contain AMR and Chapter 6.10 of the OIE Terrestrial Code also include the elements that should be taken into consideration in the regulation of preclinical trials, to ensure the efficacy of the VMP and establish an appropriate dosage regimen that ensures efficacy and contains AMR development. Most countries will not include this level of detail in their national legislation, as these requirements are subject to continuous scientific update and require flexibility to be updated to align with the relevant international standards. For those countries that include

[15] Post-marketing antimicrobial surveillance. According to the OIE Terrestrial Code, Chapter 6.10, Article 6.10.3, para. 8 "The information collected through existing pharmacovigilance programmes, including lack of efficacy, and any other relevant scientific data, 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 microorganisms resistant to antimicrobial agents is essential. The relevant authorities should implement a programme in accordance with Chapter 1.4;
b. Specific surveillance
   Specific surveillance to assess the impact of the use of a specific antimicrobial agent may be implemented after the granting of marketing authorisation. The surveillance programme should evaluate not only resistance in target animal pathogenic agents, but also in food-borne pathogenic agents, and commensals if relevant and possible. This will also contribute to general epidemiological surveillance of antimicrobial resistance."

requirements for preclinical trials into documents of legal nature (regulations, technical standards, procedures), it is important to verify their compliance with the international reference standards.

Finally, the Competent 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.

Use

Legislation may establish restrictions or prohibitions related to the use of AMs for non-therapeutic purposes.[16] An example of this could be the prohibition to use AMs for growth-promotion, or the approval of lists of essential medicines, medicines restricted for human use or last resort antibiotics. Similarly, legislation should serve as basis to introduce restrictions related to group administration of AM for selected species or products.

Legislation should pay attention to professionals that are authorized to prescribe, sale and administer AMs, including the necessary background, training and capacity. There should be specific provisions for veterinarians (or other qualified professionals authorized to prescribe VMPs in national legislation) to: (i) be the only ones with the authority and responsibility to prescribe specified AMs (including antibiotics), and only for animals under their care;[17] (ii) be accountable for the prescriptions they issue, as well as to record and report on all prescription of specified AMs; and (iii) monitor the use of AMs and report to the competent authorities information on prescription and use, as well as any potential adverse or abnormal effect. VMPs should only be supplied through licensed or authorized distribution systems and administered by a veterinarian or under the supervision of a veterinarian or an authorized person (OIE, 2019b, Article 6.10.3, para. 9).

These provisions would function to ensure veterinary oversight and accountability on the use of AMs, as well as to collect the detailed information on AMs prescribed or administered to animals to serve as the basis for benchmarking usage levels on farms and/or prescription patterns of veterinarians.

Additionally, legislation should include provisions to prevent, monitor and control substandard and falsified veterinary medicinal products, and it should determine penalties for cases of contravention. The use of substandard drugs leaves animals inadequately protected from disease, promotes the evolution of drug-resistant strains of bacteria and can pose a risk to human health where harmful chemical residues enter the food chain. A number of countries have introduced specific provisions related to falsified and substandard medicinal products in their veterinary medicinal products legislation. For example, there are a number of prohibitions under §331 of the Federal Food, Drugs, and Cosmetic Act of the United States addressing this issue, such as prohibiting the "[f]orging, counterfeiting, simulating, or falsely representing, or without proper authority using any mark, stamp, tag, label, or other identification device authorized or required by regulations…". Other regulatory solutions may include adopting provisions on falsified and substandard medicinal products in general veterinary legislation, general medicinal products legislation, consumer protection legislation, product integrity legislation, and quality of agricultural and veterinary input legislation. Importantly, legislation

[16] Note that this is referred to as "non-veterinary medical use of antimicrobial agents" in Article 6.9.2 of the OIE Terrestrial Code, and is defined as the "administration of antimicrobial agents to animals for any purpose other than to treat, control or prevent infectious disease; it includes growth promotion".

[17] Codex Code of Practice to Minimize and Contain Antimicrobial Resistance (CAC/RCP 61-2005), Section 48, specifies that veterinary antimicrobial drugs should only be prescribed for animals under the veterinarian's care, meaning:
- the veterinarian has been given [real, not nominal] responsibility for the health of the animal(s) by the producer/producer's agent;
- the animal(s) has been seen immediately before the prescription and supply, or recently enough for the veterinarian to have personal knowledge of the condition/health status of the animal(s) to make a diagnosis and prescribe;
- the veterinarian should maintain clinical records of the animal(s).

should also give national authorities the responsibility and the powers necessary to enforce such provisions.

Advertising

Regulatory control should take into consideration the content of advertising material. Indeed, a VMP is a health product (not an ordinary product), which justifies a regulatory framework limiting advertising and promotion to the minimum necessary and primarily for medical information. Misleading claims or advertisement that could modify consumers' behaviour should be strictly regulated and controlled.

Article 6.10.3, paragraph 10 of the OIE Terrestrial Code clarifies that all advertising of AM should be compatible with the principles of responsible and prudent use and should be controlled by advertising rules or standards. The relevant authorities must ensure that the advertising of these products: (a) complies with the marketing authorisation granted, particularly regarding the content of the summary of product characteristics; and (b) is restricted to a veterinarian or other suitably trained person authorised to prescribe VMP containing AM agents in accordance with the national legislation and under the supervision of a veterinarian.

Operators' responsibilities

Legislation should provide a basis for the registration or authorization of all VMPs operators, including those manufacturing, importing, storing, processing, wholesaling or otherwise distributing VMPs and biological or raw materials for use in making VMPs. Regulatory control over manufacturers and importers (through licenses, permits, inspections and reporting duties) is instrumental to gain control not only over the quality of the AM in the market, but also over their production processes and, for instance, the way in which obsolete AM are collected or contaminated residues (including waste water) are disposed. Through establishing licensing and permit requirements for the exercise of these activities the government would gain the possibility to introduce specific criteria for the authorization of the activity, as well as record-keeping and data collection and reporting obligations.

Similarly, legislation should define the responsibilities of operators in other stages of the VMP life cycle.[18] In that respect:

- Legislation should recognize producers' responsibilities regarding the judicious and appropriate use of AMs, the implementation of health and welfare programmes on their farms, the compliance with the withdrawal times of VMPs to ensure that AM residue levels in food products of animal origin do not present a risk for the consumer, and the sound disposal of waste material to minimize the development and spread of AMR.[19]
- Wholesale and retail distributors should have the responsibility to distribute and/or supply veterinary AMs only upon prescription of a veterinarian or other qualified professional authorized in accordance with national legislation (Codex Alimentarius Commission, 2005).
- Animal health workers and extension services may have a responsibility in monitoring producers' use of AMs, advising on the observance of withdrawal times and the disposal of waste from AMs and from animals treated with AMs.

[18] In this document references to the VMP life cycle refer to all stages of the production (from selection of ingredients to manufacture and packaging) of VMPs, their access, sale, distribution, transport and storage, use and disposal, including treatment of obsolete and unused VMPs, residue monitoring, and treatment of packages that are potentially contaminated with AM.

[19] This enumeration is not exhaustive, for further responsibilities, see Codex Code of Practice to Minimize and Contain Antimicrobial Resistance. CAC/RCP 61-2005, Sections 58 and 59.

Legislation should also provide rules and protocols for the safe collection, disposal and destruction of unused or obsolete VMPs containing AM. It should require their labels to have appropriate instructions for disposal and destruction (OIE, 2019b, Article 6.10.3, para. 9).

Monitoring and enforcement

To ensure efficacy of the system, legislation should recognize the power and responsibility of the competent authority to put in place monitoring and surveillance systems for AM use and disposal, as well as for AMR development, aligned with the international reference standards.

In this regard, the OIE Terrestrial Code Chapter 6.8 provides rules for the harmonization of national AMR surveillance and monitoring programs, and Article 6.10.3, paragraph 8 provides detail of post-marketing AM surveillance. The Codex Code of Practice to Minimize and Contain AMR adds that epidemiological surveillance of AMR should be accompanied by data on the amounts of VMPs used by veterinarians and other authorized users in food-producing animals collected from: manufacturers, importers and exporters, veterinarians, farmers and producers of food-producing animals.

National authorities should have pharmacovigilance programmes in place for the monitoring and reporting of adverse reactions to VMPs, including lack of the expected efficacy related to microbial resistance, and this should serve to re-evaluate the authorization of specific VMPs, if necessary.

c. Analysis of national legislation on veterinary medicinal products (antimicrobials)

Where can this be regulated?

VMPs might be regulated in stand-alone VMPs legislation, in general pharmaceuticals legislation, in general animal health and/or production legislation or in general fisheries or aquaculture legislation. In some countries, there might be separate legislation for livestock and aquaculture, including separate legislation for VMPs for terrestrial and aquatic animals. If this is the case both regulatory frameworks would need to be analysed against the questions below.

In addition, regulatory control over falsified and substandard veterinary medicinal products can be regulated in VMPs legislation, general veterinary legislation, general medicinal products legislation, consumer protection legislation, product integrity legislation, and quality of agricultural and veterinary input legislation.

What are the key elements relating to VMP regulation?

a) Definition

(i) Is there a definition for VMP? Are VMPs part of a broader definition of medicinal products?

(ii) Is there a definition for AMs/AM agents or any other variations of this term?

b) Competent authority

(i) What is (are) the competent authorities for:

i. The authorization and management of VMPs;

ii. VMPs monitoring and enforcement;

iii. Ensuring VMPs quality, safety and efficacy.

Please take into consideration all VMPs, including terrestrial and aquatic animals. If more than one institution is involved, please include all the institutions. Include a reference to the law/legal instrument where the powers of the authority are granted.

c) **Registration/authorization** of veterinary AMs

(i) Is there a list of AMs or a registry of AMs approved by the government?

(ii) Is there legislation that prohibits the production, importation, distribution, supply and use of VMPs unless they are authorized/registered according to national legislation?

Are there any exceptions to the rule? Under which circumstances?

(iii) Does legislation include some reference or mechanism to ensure transparency in decision making?

(iv) Does legislation include a reference to the need to coordinate the authorization/registration of veterinary AMs with the authorization of human AMs? Is there any provision on the need to restrict the authorization/use of AM critical for human purposes for veterinary use?

(v) Which requirements are in place for the authorization of AMs? (data requirement, efficacy tests, product indications (usage) and claims, package and labelling requirements, ADI, drug withdrawal times, stability when mixed with feed or drinking water, safety requirements, including potential effects on the intestinal flora of humans)?[20]

(vi) Are these requirements included in legislation that can be easily modified by the national authority to adapt to scientific changes? (secondary legislation)

(vii) Does legislation include a requirement that VMPs are classified according to typology, potential hazard and requirements related to prescription and supply?

d) Essential medicines list

(i) Is there legislation that refers to the approval of an essential medicines list[21] and/or a list of essential medicines for veterinary purposes? [*note that this list is different from the general registry/ general list of authorized VMPs*]

(ii) Does legislation include provisions on the restriction of certain AMs to human use only? Does it include restrictions to use essential AMs for veterinary use only as last resort and in individual treatments?

[20] See OIE. Terrestrial Code. Chapter 6.10 Responsible and prudent use of antimicrobial agents in veterinary medicine. 5. a) Establishment of acceptable daily intake (ADI), maximum residue (MRL) and withdrawal periods in food-producing animals.
[21] See the WHO model lists for essential medicines at: http://www.who.int/medicines/publications/essentialmedicines/en/.

e) Quality control

(i) Does legislation regulate the quality, safety and efficacy control of VMPs, including standard setting, monitoring and control (sampling, tests) before registration?

(ii) Does it mandate the competent authority to do monitoring and control of VMPs post-registration and in the market (*pharmacovigilance*[22]) including surveillance for adverse effects, to ensure AM agents and the VMP containing them are manufactured to the appropriate quality and purity in order to guarantee their safety and efficacy, as well as arrangements for recall?

(iii) Does legislation include specific provisions to prevent, monitor and control substandard or falsified veterinary medicinal products? Are there specific provisions for substandard or falsified medicinal products (for human or veterinary purposes)? Or, if this is not the case, are these part of general products legislation?

(iv) What is the body of inspectors in charge of enforcing legislation on substandard or falsified VMPs? If these are not veterinary inspectors, does legislation provide for the need to coordinate the fight against substandard or falsified products with veterinary inspectors?

(v) Does legislation include a provision on the designation of official laboratories (either public or private, within or outside the country) to test drugs for quality and efficacy in order to identify substandard or falsified drugs?

f) Labelling, packaging and advertising

(i) Is there legislation on the labelling of AMs that specifies:

i. their authorized use, including the species for which they are authorized and the authorized route of administration;

ii. recommended dosages;

iii. storage requirements;

iv. withdrawal periods;

v. other elements as included under III. 1) (b) of this document (Labelling).

(ii) Is there legislation on the inclusion of claims (such as health claims) in the packaging?

(iii) Is there legislation on the advertising and/or marketing of VMPs? Are false or misleading claims prohibited?

(iv) Are there restrictions on advertising restricted use VMPs only to veterinary professionals and not to the general public?

(v) Does the legislation require inclusion of expiration dates on the label?

(vi) Does the legislation require that labels be printed in local languages?

(vii) Does the legislation require that the label or package specifies that the VMP is for animal use only?

[22] See OIE Terrestrial Code, Article 6.10.3, para. 8.

g) Prescription

(i) Does legislation prohibit the sale or dispensing of AMs (or a selected list of AMs) without prescription?

(ii) Does legislation specify that only veterinarians (or authorized professionals) can prescribe AMs? Is this restriction specific in that such persons may only issue prescriptions to animals under their care on the basis of a veterinary diagnosis?

(iii) Are veterinarians (or authorized professionals) mandated to only prescribe AMs for animals under his/her direct care?[23] [*note that this could be included under VMPs legislation, animal health or veterinary profession/statutory body legislation]*

(iv) Are veterinarians held responsible and accountable for their prescription and use of AMs?

(v) Are veterinarians required to keep records and report information on the prescription of AMs? Does the competent authority (or the veterinary statutory body) have the mandate and capacity to request this information from all veterinarians (public and private)? Are there any provision relating to confidentiality of such records and how such data can be used by the authorities or other persons with access?

(vi) Are there any provisions that allow the off-label or extra-label use of veterinary medicinal products? If so, under what conditions?

h) Sale

(i) Where can AMs be sold? Can AMs be sold only in pharmacies and veterinary clinics or also in other establishments (such as feed distributors, supermarkets or pet shops)? Is there any differentiation in the types of AMs that can be sold by the different types of sellers?

(ii) Is a specific license/permit or other authorisation process required for a person to sell AMs?

(iii) Can AMs be sold directly by veterinarians? Is this regulated? If so, are there mechanisms to safeguard against potential conflict of interest?

(iv) Are pharmacies and other establishments or professionals that sell AMs legally required to keep and report records of the sale of AMs? Does this requirement explicitly state what information must be recorded?

(v) To whom can AMs be sold? Are there any restrictions?

(vi) Is there a prohibition to sell any of the following: unlabelled, unregistered, substandard or falsified products?

(vii) Are there provisions or reference to standards on the storage of AMs?

(viii) Are there requirements on safe disposal for unused and expired VMPs?

(ix) Does legislation contain penalties associated with selling VMPS in a manner contrary to the law? Are there specific provisions making it illegal to sell VMPs without the required prescription, or to sell counterfeit or substandard VMPs?

[23] See Codex Alimentarius. 2005. Codex texts on foodborne antimicrobial resistance: Guidelines for risk analysis of food borne antimicrobial resistance (CAC/GL 77-2011), 2011; Code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005). Responsibilities of Veterinarians, p. 11.

i) Use

(i) Are there rules on how AMs can be used?

(ii) Are there any provisions on oversight or supervision by a veterinarian or other veterinary professional in the administration or use of certain VMPs?

(iii) Are therapeutic and non-therapeutic uses of AMs differentiated? How are they defined?

(iv) Is there a prohibition or restriction to use AMs for non-therapeutic purposes such as for growth promotion or productivity? Does legislation point to any protocols for risk criteria for diagnosis for disease prevention uses in animals and agriculture

(v) Is there any restriction in legislation [or codes of conduct?] that restrict the use of medically important AM (CIAs) in animals?

(vi) Are the terms prevention, control and treatment defined in national legislation?[24]

(vii) Are there any limitations on the use of AMs for any therapeutic purposes? Are they limited on the basis of a risk assessment?

(viii) Does legislation require AMs be administered to animals by a veterinarian or under the supervision of a veterinarian or by other authorised persons?

(ix) Are livestock/aquaculture producers legally required to keep records of the AMs they use and to report them to the national authorities? And to permit and facilitate the taking of samples?

(x) Are livestock/aquaculture producers legally required to return unused or obsolete AMs? Are there other legal provisions related to the disposal of unused or obsolete AMs?

j) Manufacturing

(i) Is there legislation on production procedures and requirements for the pharmaceutical industry to ensure quality standards? [*this could be included in licenses to manufacturers/pharmaceutical companie*s]

(ii) Is there a system of registration or authorization for VMPs manufacturers (pharmaceutical companies)?

(iii) Are operators manufacturing VMPs legally required to keep records of the AMs they produce and to report them to the national authorities?

(iv) Is there legislation on production procedures and requirements for the pharmaceutical industry to minimize environmental contamination with AMs resulting from the production process?

(v) Is there legislation prohibiting or restricting repackaging of AMs?

[24] These terms are defined by the OIE in Chapter 6.9. of the Terrestrial Code on "Monitoring of the quantities and usage patterns of antimicrobial agents used in food-producing animals", as follows: (i) to 'treat' means to administer an antimicrobial agent to an individual or a group of animals showing clinical signs of an infectious disease; (ii) to 'control' means to administer an antimicrobial agent to a group of animals containing sick animals and healthy animals (presumed to be infected), to minimise or resolve clinical signs and to prevent further spread of the disease; (iii) to 'prevent' means to administer an antimicrobial agent to an individual or a group of animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the drug is not administered. See http://www.oie.int/en/for-the-media/press-releases/detail/article/oie-general-session-three-new-steps-in-the-fight-against-antimicrobial-resistance/.

(vi) Is there legislation on how to treat waste resulting from the production of AMs?

2) Animal health and production practices to prevent animal disease in terrestrial and aquatic animals

a. Background

Appropriate animal health management, with a focus on disease prevention, can contribute towards reducing the need for AMU and minimizing the development and spread of AMR. Good veterinary legislation, aligned with the international reference standards approved by the OIE, can have a positive impact on disease prevention. Veterinary legislation is also necessary to recognize the mandate and functions of the veterinary authority and to implement the "chain of command", where the responsibilities and powers of the authority, from the central level to those implementing legislation in the field is clearly defined, and the veterinary authority is able to approve and enforce animal health measures directly in the whole territory of the country. Veterinary legislation should, among other measures, include the possibility for the veterinary authority to restrict animal movements and approve and implement animal health measures. Comprehensive legislation on veterinary professions can also contribute to ensure that AMs are prescribed by qualified professionals.

In addition to animal health legislation, good animal husbandry and feeding practices can benefit animal health and have a positive impact on reducing the use of AMs. Animal health and animal welfare legislation may include animal welfare standards that would support improving living conditions of livestock and aquatic animals and reducing diseases. Other activities within the realm of animal production and rearing that may deserve regulation include the use of manure from treated animals as fertilizers, as this could spread both AM residues and resistant microorganisms.

b. Analysis of veterinary legislation

Where can this be regulated?

Veterinary legislation is defined by the OIE as "laws, regulations and all associated legal instruments that pertain to the veterinary domain" (OIE, 2019c), which is understood as "all the activities that are directly or indirectly related to animals, their products and by-products, which help to protect, maintain and improve the health and welfare of humans, including by means of the protection of animal health and animal welfare, and food safety" (OIE, 2019b, Article 3.4.2). This may include animal disease control legislation, general animal health and/or production legislation, fisheries and aquaculture legislation, among other legal instruments.

Animal production and production practices may be regulated through general agriculture legislation, in veterinary legislation or in stand-alone animal production legislation or animal welfare legislation. In some countries, the specific production practices would not be included in legislation, but in implementing regulations or non-binding guides or manuals. In these cases, it is important to pay attention to the framework legislation that serves as the basis for the development and implementation of these regulations and documents.

What should be identified?

Animal Health

a) Is there legislation that identifies the competent veterinary authority and gives it the mandate to implement the legislation? Does this legislation recognize or facilitate the implementation of the "chain of command"?

b) Does legislation contain a clause on the possibility for the national veterinary authority to delegate some functions?

c) Does the veterinary authority have the mandate to restrict or regulate the movement of animals and animal products? (including movement permits, declaration of areas as infected areas, control areas and free areas (compartmentalisation), etc.)

d) Does the veterinary authority have the mandate to approve surveillance plans, including sampling and analysis? Is there an obligation for laboratories to share data on surveillance with other reference, official and authorized laboratories or government entities?

e) Does the veterinary authority have the mandate to approve other animal health measures, including control plans, quarantine, compulsory treatment or vaccination, animal culling and compensation? Does legislation specify that these measures must be risk based?

f) Does legislation include the mandate of the national veterinary authority to approve a list of notifiable diseases based on the OIE list of diseases?[25] Does legislation contain the obligation of notification of notifiable diseases?

g) Does the veterinary authority have the mandate to establish an early warning system, prepare a contingency plan and undertake emergency action for diseases and pathogen outbreaks?

h) Does the veterinary authority have the mandate and the possibility to declare an animal health emergency and to adopt and implement risk-based emergency measures?

i) Does legislation recognize the responsibility of farmers to maintain the health status of their animals, keep records, notify potential diseases and implement biosecurity measures?

j) Does legislation establish a system for animal identification and traceability?

k) Does the veterinary authority have the mandate to monitor and enforce veterinary legislation, including the powers of veterinary inspectors to enter into private properties, take samples and review records?

l) Does the veterinary authority have the mandate to designate and regulate reference, official and authorized laboratories?

m) Does legislation contain provisions on the sharing of information and data among laboratories and between these and the surveillance authorities? Does the competent authority have the right to request for AMR-related information to reference, official and authorize laboratories, as well as other entities undertaking AMR surveillance?

n) Does legislation give the national veterinary authority the mandate to approve import requirements that are risk based, and/or take into consideration the international reference standards? Does it require that the international trade of animals and animal products be accompanied by an international veterinary certificate issued by the national veterinary authority?

o) Is there national legislation on veterinary professions that specifies who can practice veterinary medicine, and the obligations and responsibilities of veterinarians? Does this legislation refer to the qualification necessary to prescribe AMs?

[25] The OIE list of terrestrial animal diseases is included in Article 1.3.1 of the OIE Terrestrial Code, available at http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_diagnostic_tests.htm. The OIE list of aquatic animal diseases is included in Article 1.3.1 of the OIE Terrestrial Code, available at http://www.oie.int/index.php?id=171&L=0&htmfile=chapitre_diseases_listed.htm.

Animal production

a) Is there animal welfare legislation, including good husbandry practices?

b) Are there legal requirements for farmers on unused AMs?

c) Are there Good Husbandry Practices (GHP), Good Production Practices (GPP) or guidelines for farms, slaughterhouses, wet markets, healthcare facilities and veterinary care facilities to minimize the transmission of microbes or contamination with AMs?[26] Are these reflected in legislation?

d) Are there GPP/GHP for fish/meat/dairy processing units to minimize the transmission of microbes or contamination with AMs?[27]

   More specifically, are there GPP/GHP that recommend or require:

   (i) Prohibition on the use of manure from animals being treated with AMs as fertilizer;

   (ii) Prohibition on the use of products or by-products from animals being treated with AMs for animal production (such as milk for young animals);

   (iii) Good practice on the disposal of animal products and by-products from animals treated with AM, as well as water and other waste resulting from cleaning treated animal production premises;

   (iv) Appropriate storage and disposal of AMs in the farm;

   (v) Good practices on how to use AMs in drinking water systems.

e) Is there legislation on health and safety at the workplace that would be applicable to farms? Could this legislation serve to protect farmers from the risks associate to exposure to AMs and AMR bacteria?

3) Feed legislation

a. Background

Animal feed may include ingredients and additives with AM properties. These could include VMPs in medicated feed, for therapeutic or non-therapeutic purposes, and other additives that might not be considered as VMPs, but still have an AM effect (including some substances and ingredients) creating potential for AM contamination and AMR.

Medicated feed[28] contains VMPs (including AMs) and is used for treating sick animals, for animal disease prevention and for growth promotion. Their use is particularly extensive in intensive production systems to prevent the spread of disease. Medicated feed is frequently produced and sold under the same regulatory framework as regular feed.

Different AMs can be included as additives to feed, including antibiotics, antivirals or antiparasitics (coccidiostats, wormers). Countries and international organizations may consider these AM substances

[26] As this is not necessarily a legal question, you would need to address this question in your meetings with the veterinary authority. Even if there is no specific legislation, good practices approved by the veterinary authority may be relevant within the broader regulatory framework.

[27] See previous footnote. Such practices might be included in legally binding or non-legally binding instruments. In the latter case, the practices may be given regulatory value through reference in legally binding instruments. The information can be collected from the national authorities in charge of aquaculture or VMPs.

[28] Codex Alimentarius. Medicated Feed: Any feed which contains veterinary drugs as defined in the Codex Alimentarius Commission Procedural Manual. Code of Practice on Good Animal Feeding. CAC/RCP 54-2004. Retrieved from: http://www.fao.org/docrep/012/i1379e/i1379e06.pdf.

differently. As an example, the OIE definition of AM (OIE, 2019c) specifically excludes "anthelmintics and substances classed as disinfectants or antiseptics". In the EU, most coccidiostats and histomonostats are included within the scope of the Regulation (124/2009) on feed additives. It is important to clarify what is defined as "medicated feed" and "feed additives" in national legislation, with special attention to antiparasitics.

In combatting the risks posed by AMR, legislation should distinguish medicated feed from feed that does not contain VMPs, and consider imposing stricter controls on the production, distribution, and use of medicated feed. In fact, it is useful that medicated feed is considered as a regular VMP and subject to the same rules regarding use, sale, record keeping and disposal.

In addition to the regulation of medicated feed, other elements of feed legislation could also have an impact on AMR. An example of that is the regulation of feed ingredients and additives that can be incorporated to feed. Additives such as zinc, silver or copper may have AM effects, the residues of these additives in the manure of animals that have ingested the substances may result in the contamination of soil and water, which could pose AMR risks. Thus, identification of the regulatory mechanism for the authorization, restriction or prohibition in the use of specific additives in feed production would be relevant for AMR.

Another area of interest relates to animal nutrition, and what should/could be incorporated to feed to improve the animal health status and its resistance to disease. Different legal mechanisms can help governments to introduce feed quality and nutrition requirements, such us establishing minimum nutritional requirements for feed products to be registered or regulating the use of health claims or labelling information for feed ingredients and substances that might positively contribute to improve the animal health status.

b. Analysis of legislation on feed

Where can this be regulated?

Feed can be regulated in stand-alone feed legislation, in food safety legislation, in general veterinary (animal health or production) legislation, VMP legislation, or in more general agriculture inputs or agriculture legislation, as well as in fisheries or aquaculture legislation.

What should be identified?

Medicated feed

a) Under which legislation is medicated feed regulated?

b) Is there a definition of medicated feed? Does this include, (or expressly exclude) all or some antiparasitics?

c) Is medicated feed subject to similar requirements (of authorisation, prescription, sale and use) than regular medicinal products?

d) Are there prohibitions or restrictions to the production, sale, import and use of medicated feed?

e) Is the use of medicated feed for non-therapeutic purposes (such as growth promotion) prohibited or restricted?

f) Is there legislation that prohibits the dispensing or sale of medicated feed in feed mills or feed establishments without a prescription from a veterinarian?

g) Are there specific requirements (in connection with the licensing and registration process or other aspect) relating to manufacture or production relating to the mixing of AMs/VMPs into feed?

h) Are there provisions to prevent contamination from medicated feed (or feed containing AM substances) to other feed products? (e.g. cleaning methods, double production lines etc)

i) Does medicated feed require prescription by a veterinarian? Does medicated feed require oversight or administration by a veterinary professional?

j) Are there record-keeping obligations related to the prescription and use of medicated feed?

k) What are the labelling requirements for medicated feed? Are there provisions that require specific instructions and information be given for the correct and safe use of medicated feed?

Feed additives

l) Is there a definition of feed additive or just "additive"?

m) Is there a regulatory mechanism to approve, authorize, restrict or prohibit the use of additives in feed production?

n) Are claims of "health" or "growth" allowed in legislation for feed additives that are not VMPs but that may have a positive impact on animal health (such as probiotics)? If so, what are the requirements to allow for these claims?

4) Pesticides

a. Background

Pesticides are utilized extensively in agricultural production, forestry and the environment. Pesticides are defined by the International Code of Conduct on Pesticide Management (ICCPM) as any substance, or mixture of substances of chemical or biological ingredients intended for repelling, destroying or controlling any pest, or regulating plant growth (WHO and FAO. 2014). This broad definition includes all chemical and organic substances used to contain pests, including substances with AM effects. This is particularly the case for pesticides with AM effects that are used for plant purposes as well as for human or animal purposes.

The ICCPM recommends countries to regulate all pesticides together, including chemical and biological pesticides, for agriculture or pest control (such as malaria control), for plant and livestock use. The ICCPM is implemented through a number of Guidelines[29] that include the Guidelines on Registration (FAO and WHO, 2017) and the Guidelines on Pesticide Legislation (FAO and WHO, 2015b), among others. Following these Guidelines, no pesticide should be placed on the market unless it is registered as prescribed. Also, all pesticides should be registered following a risk-analysis based procedure that takes into account environmental, human health and agronomic considerations. These considerations should be clearly indicated in implementing national legislation. Pesticides should be labelled with due consideration of the international guidance documents,[30] including their directions for use, hazardous information, precaution measure, pre-harvest interval etc. The ICCPM advocates for a sound management of pesticide through their whole life cycle (from cradle to grave) that includes pesticide registration, pesticide use, licenses and permits to specific activities (transportation, storage, import), pesticide disposal and the management of empty containers, unused and obsolete pesticides. Finally, the maximum residue limits (MRLs) of pesticides in food and feed are normally regulated under food safety legislation (see section 5 below).

Therefore, the focus of the regulatory control in the pesticide domain should be the registration/authorization or use of pesticides with AM effect in the prevention or control of pests. This

[29] These guidelines are available at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/code/list-guide-new/en/.

[30] The ICCPM refers to the Globally harmonized system of classification and labelling of chemicals (GHS) as reference for pesticide labelling. See Guidelines on Good Labelling Practice for Pesticides at http://www.fao.org/3/a-i8091e.pdf.

could be done by prohibiting, restricting or limiting the use of certain pesticides with AM effect, or by introducing additional guarantees in the use of such products (special licenses, permits or reporting duties).

b. Analysis of legislation relevant for pesticides management

Where can this be regulated?

Pesticides can be regulated under specific pesticide legislation, under general agricultural legislation or public health legislation (for household pesticides and pest control treatments such as malaria). They are sometimes regulated under general plant protection laws that include the management of pesticides, or under general chemicals legislation that cover also pesticides of chemical origin. Veterinary pesticides could be included under general VMP legislation.

What should be identified?

(i) Does the country have legislation on the authorization and registration of pesticides? What is the scope of such legislation?

(ii) Is the scope of the law broad enough to cover pesticides used for public health and livestock production purposes (insecticides and antiparasitics)?

(iii) For the registration or authorization of pesticides, do the authorities have the possibility to take AMR considerations into account in their decision making? [*There might not be something specific, but if decision making can take into consideration different criteria, that would be sufficient*]. Are there provisions on pre-harvest intervals following pesticide application?

(iv) Are there licensing mechanisms related to specific pesticides activities (such as the sale, import, export, transport or special uses of pesticide (such as drift control in aerial fumigation))?

(v) Are there provisions on pesticide labelling? Do they follow the recommendations of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS)[31]?

(vi) Are there requirements for the advertisement of pesticides?

(vii) Are there requirements for the management and disposal of used pesticide containers?

(viii) Are there requirements for the safe disposal of unused or obsolete pesticides?

5) Food safety

a. Background

Animal products may contain high levels of residues of AMs when the withdrawal periods have not been respected or following intensive treatments. The residues could be passed through the food chain when the animal products are consumed and could lead to further development and spread of resistance.

The Codex Alimentarius Commission recommends the Maximum Residue Limit for Veterinary Drugs (MRLVD) to be legally permitted or recognized as acceptable in or on a food (definitions adopted by the

[31] GHS are available at https://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf.

Codex Alimentarius Commission - Codex Procedural Manual)[32] and has determined standards denoting the acceptable MRLVD for food safety purposes. These MRLVD are defined as the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg /kg on a fresh weight basis) (Codex Alimentarius Commission, 2018a).

Similarly, food could also contain residues of pesticides. The MRL for pesticides has been defined by Codex Alimentarius Commission as the "maximum concentration of a pesticide residue (expressed as mg/kg), recommended by the Codex Alimentarius Commission to be legally permitted in or on food commodities and animal feeds" (Codex Alimentarius Commission, 2020c). MRLs are based on Good Agricultural Practice in the Use of Pesticides data and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable.[33]

Water and other drinks are also included in the Codex Alimentarius definition of "food"[34] and should be subject to the same maximum residue limits of veterinary medicinal products and pesticides for food safety.

Additionally, some food additives with AM effects could contribute to the spread of resistance when they are used in food production and/or disposed to the environment. This can be the case for some disinfectants, fungicides and other additives approved both as additives in food, or to ensure hygiene in food production. Governments should have the capacity and mandate to analyse, prohibit or restrict the use of food additives that may result in the development or spread of AMR, and this should be reflected in legislation.

From a point of view of prevention, countries should put in place an effective food safety system enshrined in appropriate food safety legislation in order to improve the food safety status and reduce food safety risks and the need for AM. This section contains some of the key elements of a modern food safety system based on international reference standards and best practices.

b. Analysis of food safety legislation

Where can this be regulated?

Food safety can be regulated in specific food safety legislation, in more general public health codes, or in specific legislation with a different scope, such as food and drugs legislation. Provisions

[32] Codex Alimentarius Glossary of Terms and Definitions (Residues of Veterinary Drugs in Food), Maximum Residue Limit for Veterinary Drugs (MRLVD). It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects. When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available. CAC/MISC 5-1993, retrieved from http://www.codexalimentarius.org/download/standards/348/CXA_005e_u.pdf.

[33] According to the Codex Alimentarius (Pesticide Database Glossary), "Codex MRLs which are primarily intended to apply in international trade, are derived from estimations made by the JMPR [Joint FAO/WHO Meeting on Pesticide Residues] following: a) toxicological assessment of the pesticide and its residue; and b) review of residue data from supervised trials and supervised uses including those reflecting national food agricultural practices. Data from supervised trials conducted at the highest nationally recommended, authorised or registered uses are included in the review. In order to accommodate variations in national pest control requirements, Codex MRLs take into account the higher levels shown to arise in such supervised trials, which are considered to represent effective pest control practices. Consideration of the various dietary residue estimates and determinations both at the national and international level in comparison with the ADI, should indicate that foods complying with Codex MRLs are safe for human consumption." Explanation retrieved from http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/pestres/glossary/en/.

[34] As discussed in the Codex Alimentarius Commission, 2018b p. 23, food means "any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of 'food' but does not include cosmetics or tobacco or substances used only as drugs."

related to food safety and quality could also be contained in general consumer protection legislation.

MRLs are most frequently regulated in food safety legislation. They could also be addressed in VMP legislation or in general public health legislation. In some countries, veterinary or fisheries legislation may contain provisions on MRLs. Finally, some countries may regulate their MRLs through binding or non-binding technical standards or regulations approved in the framework of food safety, standard setting or other food-related legislation.

Food additives, and the procedure to approve or restrict the use of a food additive, are also most frequently regulated in food safety legislation. This can also be regulated in standard-setting legislation, health legislation or industrial processes legislation.

What should be identified?

Food safety system

a) Is there a national legislation governing food safety? Which legal instruments regulate food safety?

b) Does legislation establish a national competent authority or authorities to coordinate food safety in all stages of the food production chain?

c) Does legislation contain a provision on the possibility for this authority to delegate some functions?

d) Which is (are) the national institution(s) with a mandate on food safety across the different stages of the food chain? Is there a mechanism for coordination across the different institutions with a role on food safety?

e) Does the national authority (or the authorities) have the mandate to approve measures to prevent, identify and control food hazards? (that may include microbial or AM contamination).

f) Are they mandated to approve, monitor and control food safety and quality standards based on Codex standards?

g) Does legislation recognize the primary responsibility of food operators for food safety? Are there mechanisms to keep food operators under regulatory control (such as registration, licenses or permits)?

h) Does the food safety authority have the mandate to conduct surveillance programs to identify food hazards? (including microbiological contamination)

i) Does the food safety authority have the legal mandate to designate and regulate reference, official and authorized laboratories? Is there an obligation for laboratories to share surveillance data with other reference, official and authorized laboratories or other entities undertaking AMR surveillance? Does the competent authority have the right to request for AMR-related information to reference, official and authorize laboratories, as well as other entities undertaking AMR surveillance?

j) Does legislation include provisions of food traceability and recall? Does it include references to a rapid alert system to declare a food outbreak/emergency and to adopt risk-based food safety measures to contain the outbreak?

k) Does national legislation provide the mandate to the food safety authority(ies) to approve risk-based import requirements? And to certify food for export?

MRLs

l) Is there legislation on the monitoring and control of MRLs of VMPs and pesticides in food?

m) Is it compulsory to set up MRLs for all authorized AMs?

n) Are MRLs aligned with Codex?

Food additives

o) Is there a regulated procedure to approve food standards (please describe)? Does this procedure indicate that food standards should be based on Codex standards?

p) Does the competent authority have the capacity to prohibit, restrict or control the use of a food additive at any time?

6) Environment, Soil and Waste

a. Background

Legislation can serve to set up regulatory mechanisms to prevent direct or indirect contamination of the environment with AM residues and AMR bacteria. To this purpose, it is important to identify the activities that may result in release of AMs into the environment, as well as resistant organisms. Used containers for AMs may also risk exposing the environment to AMs. Attention should also be paid to indirect contamination of the environment (such as wild animals) with AM residues used, for instance, to control forest pests.

There are different manners in which environment-related legislation may have an impact on or contribute towards curbing AMR.

Some jurisdictions require an environmental impact assessment or a waste management plan as part of the authorization procedure for activities that may cause an environmental impact or include environmental audit requirements for existing installations. In this sense, environmental impact assessments might be required for the authorization of feed mills, pharmaceutical companies and laboratories (that produce or test medicinal products) and farms or other livestock businesses (markets, slaughterhouses or other animal gathering facilities). This would introduce a regulatory mechanism that enables the government to ensure facilities have appropriate mechanisms to minimize the risks of AMR.

Other examples of environmental and waste management-related legislation that could introduce AMR criteria are the regulations on the use of sewage sludge and reuse of wastewater in agriculture. This could introduce a requirement to treat sewage and wastewater that could potentially be contaminated with AM or with AMR bacteria. Soil quality legislation could pay attention to the substances used in agriculture or otherwise released into the environment, and their potential contamination with AM or AMR bacteria.

b. Analysis of legislation relevant for the environment, soil and waste

Where can this be regulated?

Environment-related legislation, specific waste legislation, natural resources protection legislation (wildlife, forestry), water quality legislation, soil legislation, noxious or pollutant activities legislation, business authorization legislation, agriculture legislation.

What should be identified?

a) In environmental protection or waste legislation, are there mechanisms that enable the authority to regulate wastewater and/or waste disposal?

b) Is there specific legislation or standards regulating the disposal of waste (including wastewater) from hospitals, medical centres, or other establishments where AMs are produced, stored or used?

c) Is there specific legislation or standards regulating the disposal of waste from farms, animal markets, slaughterhouses, quarantine facilities and other establishments where animals might be produced or kept?

d) Is there legislation where the authorities can approve certain requirements or criteria for registration of farms (or approval to carry out other activities) that are environment-related? Do they have to present an environmental impact assessment (EIA) for registration?

e) Is there legislation on soil quality, monitoring residues in soil or prevention of soil and water contamination that would cover contamination with AMs?

f) Are there regulations on antibiotic residues in effluents and waste from industries, mills, farms and other animal gathering businesses?

7) Water quality

a. Background

Water used for agriculture, livestock production or aquaculture might be contaminated with residues of AMs or resistant materials/organisms, contributing towards the development and spread of AMR. Fisheries and aquaculture legislation may contain provisions on water quality to determine the location of aquaculture activities and to prevent unacceptable levels of such pollutants in fishery and aquaculture products. Fisheries and aquaculture legislation may contain provisions to prevent water pollution during capture and production.

General water law may include references to quality control, residue monitoring, or regulatory mechanisms for the government to regulate these areas. Specific activities within a certain distance from water sources may also be regulated. If the competent authority in charge of water for irrigation has the power to monitor water used in agriculture and verify maximum limits of AMs, as well as the microbial content of the water, this would give such authority regulatory power to have oversight and control over the water-related risks of AMR.

b. Analysis of legislation relevant for water quality

Where can this be regulated?

In addition to specific water protection legislation or water quality legislation and their associated standards, water quality issues may also be addressed in general environment-related legislation, natural resources protection legislation, noxious or pollutant activities legislation or business (including farms) authorization legislation.

What should be identified?

a) Is there legislation controlling water quality, drinking water quality, environmental water quality and/or recreational water quality?

b) Is there legislation to control the quality of water used in agriculture, including aquaculture?

c) Are there legislation or standards concerning the reuse of wastewater for agricultural purposes?

d) Is there legislation on the use of AMs in aquaculture establishments in open water or in flow-through systems?

e) Is there legislation that places restrictions on the types of activities (industrial, agricultural) that can be carried out in or near water sources?

f) Is there legislation controlling the types of discharges and pollutants that can be released into freshwater resources, including watercourses, lakes and aquifers? Could this be used to introduce AMR considerations? This may be already covered in section 6 on the environment and waste, but if such provisions have not been identified in section 6, please check for relevant provisions in water and water quality-related legislation.

8) Plant Health

a. Background

Appropriate pest surveillance can help countries contain the occurrence and spread of plant pests[35] and thereby reduce the need for AMs in plant production, as well as to contain the development of resistance to plant pesticides. The International Plant Protection Convention (IPPC) was established with the main purpose of securing common and effective action to prevent the spread and introduction of pests of plants and plant products, and to promote appropriate measures for their control. The IPPC provides member countries with obligations in relation to the structure and operational principles of their phytosanitary systems. The International Standards for Phytosanitary Measures (ISPM) approved by the Commission of Phytosanitary Measures (CPM), the governing body for the IPPC, provide countries guidance to establish and operate phytosanitary systems, identify, monitor and control pests in their territories and in the international exchange of goods.

Plant health legislation implements the provisions of the IPPC into national legislation. Sound plant health legislation aligned with the IPPC and its ISPMs can help countries strengthen their phytosanitary status and reduce the need for AM. Countries which are not signatory members to the IPPC may also use the IPPC and its implementing standards as a benchmark to set up their national legislation on plant health.

Plant health legislation can contribute to combat AMR by preventing the introduction of pests in the first place so that there would be no need for further control. However, if a need arises, then contingency plans, containment and eradication programmes, use of integrated measures in the systems approach, phytosanitary treatments, pest reporting, emergency measures and other phytosanitary measures that would be based on the ISPMs could facilitate reducing the risk of development of AMR.

b. Analysis of legislation relevant for plant health

Where can this be regulated?

Most countries have special legislation on plant health that assists to fulfil their obligations under the IPPC and/or to comply with the ISPMs. However, plant health might also be regulated under broader biosecurity legislation, sanitary and phytosanitary (SPS) legislation or agriculture legislation. Some countries may regulate plant health together with pesticides for agriculture purposes under plant protection legislation, but this often causes confusion as plant protection legislation normally covers pesticide regulation, which is outside of the mandate of the IPPC. Some of the plant health related issues might be also covered under the environmental and customs legislation.

[35] The International Plant Protection Convention (IPPC) defines a pest as ¨any species, strain or biotype of plant, animal or pathogenic agent injurious to plants or plant products" (Article II), retrieved from https://www.ippc.int/static/media/files/publications/en/2013/06/06/1329129099_ippc_2011-12-01_reformatted.pdf.

What should be identified?

a) Does the country have national legislation implementing the IPPC and its ISPMs?

b) More specifically, is there a designated National Plant Protection Organization (NPPO)[36] or responsible body for plant protection?

c) Is the NPPO or responsible body for plant protection mandated to regulate and control plant pests both internally (in cultivated plants and wild flora) and in the international consignments of plants, plant products or other regulated articles[37] through surveillance, pest risk analysis, import, export and transit control, treatments, inspections, designation of areas as free from a pest, infected areas or areas of low pest prevalence?

d) Is the NPPO or responsible body for plant protection mandated to issue phytosanitary certificates and ensure the phytosanitary security of the consignment upon delivery?

e) Does plant health legislation require that plant, plant products and regulated articles imported into the country undergo a pest risk analysis prior to import? Does it require that technically justified phytosanitary requirements are put in place and, if necessary, that consignments are accompanied by a valid phytosanitary certificate issued by the NPPO or responsible body for plant protection of the exporting country?

f) Is the NPPO or responsible body for plant protection mandated to elaborate a list of regulated pests and to approve control programs to control such pests?

g) Is the NPPO or responsible body for plant protection mandated to have contingency plans in place? Is it mandated to designate reference, official and authorized laboratories?

h) Is the NPPO mandated to designate reference, official and authorized laboratories? Is there an obligation for laboratories to share surveillance data with other reference, official and authorized laboratories or government entities?

i) Does legislation contain a clause on the possibility for the NPPO or responsible body for plant protection to delegate some functions? Are there other agencies that have been mandated to perform the NPPO functions and, if yes, are those functions still under the primary responsibility of the NPPO?

j) Does legislation contain some reference to the need for coordination with other institutions (such as customs)?

9) Institutional coordination

a. Background

AMR spans across a broad range of areas, and often involves many institutions within a country that all have a role to play in addressing AMR in their domain. Specific cross-sectoral areas relevant for AMR may require several institutions to work closely together, each contributing their expertise in order to form the most appropriate and adequate regulatory response and to minimize gaps and conflicting or overlapping mandates.

[36] On National Plant Protection Organizations, see Article IV IPPC, retrieved from https://www.ippc.int/static/media/files/publications/en/2013/06/06/1329129099_ippc_2011-12-01_reformatted.pdf.

[37] The IPPC defines a "regulated article" as "any plant, plant product, storage place, packaging, conveyance, container, soil and any other organism, object or material capable of harbouring or spreading pests, deemed to require phytosanitary measures, particularly where international transportation is involved" (Article II, para. 1).

In addition, the private sector has a fundamental role to play in restricting and improving the prudent use of AMs, preventing diseases and facilitating the identification and use of alternatives to AMs, and facilitating regulatory control over all activities that may have an impact on AMU and release. In fact, there are different examples of private sector-led initiatives to reduce or control the use of AM, including self and co-regulation initiatives,[38] national action plans led by the private sector and participation in advisory or executive committees led by the public authorities.

Coordination could start at the level of the Council of Ministries or an existing cross-sectoral structure over a single Ministry (SPS single windows, sustainable production committees, etc.). It could also initiate as an informal working group among relevant Ministries. The private sector might be involved in such coordination mechanism from the beginning or it might also take the lead in proposing a structure for coordination. As regards the public entities involved, such coordinating body may formally (see below for specific legal options) or informally ensure that the relevant institutions have clear guidelines in relation to implementing their roles with AMR as an additional consideration where it is not already. Such body may be best suited to establish and oversee NAPs.

In many instances, these coordination structures will require (or benefit from) legal underpinning to be established and to operate. Such a legal underpinning could be a joint legal instrument, for example a cooperation agreement such as a Memorandum of Understanding (MoU), or a specific legal instrument. Such instruments can be signed between two competent authorities for specific cooperation, or as a group of authorities as an overarching legal basis for collaboration. Formalised coordination mechanisms could include the forming of a Committee, working group, or other arrangements that delineate the composition, the powers and responsibilities of the formalised mechanism, and the specific methods for coordination. Any coordination mechanism would need to be tailored to the specific fundamental divisions in the institutional framework of a country in order to be functional, taking into consideration the need for horizontal (across ministries) as well as vertical (between the central and the decentralized level or at one of those levels) coordination within and among governmental institutions. A certain institution may be tasked with leadership of the coordinating body.

In fact, in addition to horizontal cross-sectoral coordination, it is important to take into consideration the specific challenges of federal and decentralized countries. Jurisdictional differences also result in varying degrees of decentralization of powers and responsibilities of the governmental institutions in different countries. The national Constitution or similar basic laws of the State normally define the division of competences and responsibilities between the central level and the decentralized level (States, regions, cantons, *Länder*). Some federal systems delegate competences related to agriculture or environmental protection to the decentralized level, where the federal level maintains (or not) a certain level of oversight. Frequently, Constitutions and basic laws recognize a number of federal level competences that would override the competences of the decentralized level. This is common in areas such as national defence, international relations, and also in matters related to health hazards that may have an impact across national territories.

An example is the Prevention and Control of Infectious and Contagious Diseases in Animals Act in India. The Seventh Schedule to the Indian Constitution[39] (article 246.2) recognizes public health and sanitation as a competence in the State List. On the other hand, the concurrent list of competences includes the "Prevention of the extension from one State to another of infectious or contagious diseases or pests affecting men, animals or plants". Based on this concurrent competency, as well as on the need to

[38] Examples include countries such as Belgium, where the Antimicrobial Consumption and Resistance in Animals (AMCRA) group shifted from producing guidelines for self-regulation of the animal industry to co-regulation with the Belgian government, through the signing of a Covenant between the Federal Government and all relevant sector partners regarding the reduction in the use of antibiotics in the veterinary sector. *See* http://www.favv-afsca.be/professionnals/publications/reportamcra/_documents/2018-06-27-Publiekrapport_EN_Internet.pdf.

[39] Referred to also as the Concurrent List or List-III.

regulate transboundary diseases at the federal level[40] (the Union), this Act was approved as a federal law to be implemented by all States. Similarly, Article 149 of the Constitution of Spain includes, among the exclusive competencies of the State (Central level) (16) Basis and coordination of the national health system and legislation on pharmaceutical products. Article 148 recognizes to the Autonomous Communities (regional level) competencies on (21) Health and hygiene. It is understood that the regional level might be able to legislate within the framework (basis and coordination) established by the central level.

b. Analysis of legislation [41]

a) Is there any regulatory instrument setting up a coordination mechanism across ministries and other entities for AMR governance? (horizontal level)

b) If so, does it include all areas relevant for AMR? (consider the areas included in this report as reference)?

c) How are the composition, mandate and decision-making powers of the AMR coordination mechanism defined? Is there a reference to its funding?

d) Does this mechanism include also representatives from the decentralized level and the private sector? If it includes private sector representatives: is there any safeguard against potential conflicts of interest?

e) Is the country a federal/decentralized state? How does this impact on AMR management?

f) How are national competences shared between the central and the decentralized level for those areas relevant for AMR (health, agriculture, environment…)?

g) Does the central level have a mechanism to approve legislation (for example based on common interest) that prevails over the legislation of the decentralized level in the areas relevant for AM and AMR?

[40] See Prevention and Control of Infectious and Contagious Diseases in Animals Act, 2009. 4th: "WHEREAS it has been realised that the prevention, control and eradication of infectious and contagious diseases of animals from India has to be tackled on a national basis so as to avoid adverse impact of such diseases on the economy of the country and for this purpose harmonise the control procedures and to prevent inter-State transmission of animal diseases".

[41] Questions e) to g) might be addressed in the part of the report analysing the national legal system. If this is the case they do not need to be addressed in this section, but please make sure this is taken into consideration for the conclusions/recommendations resulting from this section.

IV. References

Bibliography

- Codex Alimentarius Commission. 2005. *Code of practice to minimize and contain antimicrobial resistance.* CAC/RCP 61-2005. Rome. 15 pp.
- Codex Alimentarius Commission. 2011. *Definitions, Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance*, CAC/GL 77- 2011. Rome. 29 pp.
- Codex Alimentarius Commission. 2017. Codex Alimentarius Commission website on: "*Ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance*". Available at: http://www.fao.org/fao-who-codexalimentarius/committees/committee/en/?committee=TFAMR
- Codex Alimentarius Commission. 2018a. Maximum residue limits (MRLs) and Risk Management Recommendations (RMRs) for Residues of Veterinary Drugs in Foods (Last modified 2018). CX/MRL 2-2018. Rome. 46 pp.
- Codex Alimentarius Commission. 2018b. Codex Alimentarius Commission Procedural Manual, Twenty-sixth edition
- Codex Alimentarius Commission. 2020a. Codex Alimentarius Commission website on: "*Index of Veterinary Drugs*". Available at: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/vetdrugs/veterinary-drugs/en/
- Codex Alimentarius Commission. 2020b. Codex Alimentarius Commission website on: "*Codex Pesticides Residues in Food Online Database*". Available at: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/pestres/en/
- Codex Alimentarius Commission. 2020c. Codex Alimentarius Commission website on "*Glossary of Terms for Pesticide Database*". Available at: http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/pestres/glossary/en/
- FAO and WHO. 2015a. *Codex texts on foodborne antimicrobial resistance*. Rome. 228 pp. Available at: http://www.fao.org/3/a-i4296t.pdf
- FAO and WHO. 2015b. *International Code of Conduct on Pesticide Management Guidelines on Pesticide Legislation*. Rome. 67 pp. Available at: http://www.fao.org/3/a-i5008e.pdf
- FAO and WHO. 2017. *International Code of Conduct on Pesticide Management Guidelines for the registration of microbial, botanical and semiochemical pest control agents for plant protection and public health uses*. Rome. 86 pp. Available at: http://www.fao.org/3/a-i8091e.pdf
- FAO. 2016. *FAO Action Plan on Antimicrobial Resistance 2016-2020. Supporting the food and agriculture sectors in implementing the Global Action Plan on Antimicrobial Resistance to minimize the impact of antimicrobial resistance*. Rome. 25 pp. Available at http://www.fao.org/3/a-i5996e.pdf
- FDA. 2012. *FDA Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*. Available at: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf
- FDA. 2013. *FDA Guidance for Industry #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209*. Available at: https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf;
- OIE. 2019. *List of antimicrobials of veterinary importance*. Paris. 9 pp. Available at: https://www.oie.int/en/for-the-media/amr/oie-amr-standards/
- OIE. 2019b. *Terrestrial Animal Health Code*. 28th Edition. Available at: https://www.oie.int/standard-setting/terrestrial-code/access-online/

- OIE. 2019c. OIE Website on "*Terrestrial Animal Health Code – Glossary*". Available at: https://www.oie.int/index.php?id=169&L=0&htmfile=glossaire.htm#terme_legislation_veterinaire
- OIE. 2020. OIE website on "*International Standards*". Available at: https://www.oie.int/international-standard-setting/overview/
- O'Neill O.J. 2014. *Review on Antimicrobial Resistance*. *Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*. The Review on Antimicrobial Resistance, Chaired by Jim O'Neill. 20 pp.
- Smith R. and Coast J. 2013: *The true cost of antimicrobial resistance*. BMJ 346, f1493.
- Soulsby. 2007. *Antimicrobials and animal health: a fascinating nexus*. Journal of Antimicrobial Chemotherapy. 60 (suppl_1): i77-i78.
- Swann MM, Baxter KL, Field HI, et al. 1969. *Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*.
- FDA. 2020. FDA Website on "*Timeline of FDA Action on Antimicrobial Resistance*". Available at: https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/ucm438426.htm
- United Nations General Assembly. 2016. *Political declaration of the high-level meeting of the General Assembly on antimicrobial resistance*, A/RES/71/3.
- WHO and FAO. 2014. The International Code of Conduct on Pesticide Management. Rome. 49 pp.
- WHO. 2015. *Global action plan on antimicrobial resistance*. Geneva. 28 pp. Available at https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/
- WHO. 2017a. *WHO list of critically important antimicrobial for human medicine (5th revision)*. Geneva. 48 pp.
- WHO. 2017b. *WHO Model List of Essential Medicines (20th List)*. 58 pp.

Legislation

- 21 USC Chapter 9, Subchapter III: Prohibited Acts and Penalties
- FDA Final Rule: Veterinary Feed Directive, 2015, https://www.federalregister.gov/documents/2015/06/03/2015-13393/veterinary-feed-directive
- Prevention and Control of Infectious and Contagious Diseases in Animals Act, 2009 no. 27, 20th March of 2009
- Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29–43
- Regulation 124/2009 of 10 February setting maximum levels for the presence of coccidiostats or histomonostats in food resulting from the unavoidable carry-over of these substances in non-target feed OJ L 40, 11.2.2009, p. 7–11.
- The Constitution of India

Legislation is essential to control antimicrobial use (AMU) and prevent antimicrobial resistance (AMR). National legal frameworks relevant for AMR contain the key regulatory controls within sectors, establish linkages among the numerous actors, sectors and activities, and facilitate coordinated implementation by the various competent authorities.

AMR spans across several sectors, from human medicine, to animal health and production, food safety and the environment. Each of these areas is governed by separate legal instruments. To strengthen national governance and regulation, it is essential that the national regulatory frameworks are analysed in a holistic, cross-cutting manner to identify the gaps and weaknesses that would likely be overlooked by considering any single sector alone.

This Methodology identifies the legal areas important for AMR in the food and agriculture sectors. It also identifies the key regulatory elements that contribute to AMR within each area. The application of this Methodology can help governments and regulators to identify gaps and deficiencies in their sectoral legislation and governance structures, improving their capacity to address AMR through legislation. The Methodology is a living document and is open to comments and suggestions.