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Regulatory frameworks to address antimicrobial resistance in the food and agriculture sectors

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Preface

Antimicrobial resistance (AMR) is a global challenge with detrimental impacts on human, animal, plant, and environmental health. The use of antimicrobials is critical for the treatment of infectious diseases and pests in humans, animals (both aquatic and terrestrial) and plants. However, the inappropriate and excessive use of antimicrobials in human health systems and in the food and agriculture sectors has exacerbated antimicrobial resistance, which refers to the inherited or acquired characteristic of microorganisms to survive or proliferate in concentrations of an antimicrobial that would otherwise kill or inhibit them. As a consequence, AMR in food and agriculture poses risks to food systems, livelihoods and economies. In addition to the direct negative impact on animals, animal diseases can significantly affect food production, food security and farmer livelihoods. Antimicrobial use in agricultural production (and through environmental dispersion of antimicrobials) contributes to the spread of AMR microorganisms and resistant genes.

Recognizing the multifaceted causes and impacts of AMR, as well as developing appropriate solutions, requires a multisectoral 'One Health' response that spans a range of sectors (including human health, the veterinary domain, agricultural production, and the environment, among others), as well as action at local, national and global levels. The One Health paradigm is a global strategy for expanding interdisciplinary collaboration and communication in all aspects of health for humans, animals, plants and the environment. The breadth of regulatory areas involved, and the rapidly evolving scientific developments that update the evidence base for policymaking, render the AMR issue a considerable regulatory challenge.

At international level, the Food and Agriculture Organization of the United Nations (FAO), the United Nations Environment Programme (UNEP), the World Health Organization (WHO) and the World Organisation for Animal Health (WOAH)[1] have developed the Quadripartite 'One Health' approach to AMR, with a range of recommendations for the responsible and prudent use of antimicrobials in all sectors. The *Global Action Plan on Antimicrobial Resistance* adopted by the World Health Assembly in 2015, invited countries to approve National Action Plans (NAPs) in line with its objectives that address AMR challenges and risks according to the individual country's needs.[2]

At country level, a comprehensive response to AMR would firstly recognize that legislation forms an essential part of the regulatory framework for antimicrobial use and can provide solutions for AMR. Policy-setting, technical and financial investment in capacity-building, and regulatory implementation are essential elements of the governance response to AMR; it is legislation that underpins all these various elements. Effective legal frameworks can help prevent the development and spread of AMR, in particular by addressing the overuse and misuse of antimicrobials, and their release into the environment. Legislation provides the force of law necessary for implementation and enforcement of NAPs and policies that address AMR. Legislation can also be used to encourage behavioural change. Institutional mandates are established by law, and thus legislation can be used to ensure coordination and collaboration of the competent authorities.

In some countries, the legal framework often fails to provide appropriate regulatory responses to the multifaceted challenges presented by AMR. Many countries have not yet assessed or reviewed their legal frameworks with the specific objective of addressing antimicrobial use and AMR. In most cases, entirely new laws are not necessarily needed; existing legislation may already offer effective provisions to adequately regulate antimicrobial use, or amendments can be introduced for this purpose. Identifying the various pieces of legislation relevant for antimicrobial use and AMR across different sectors, as well as the key

1 The World Organisation for Animal Health (WOAH) was formerly known under the acronym OIE. For the purposes of this Study, any reference made to the OIE now refers to the WOAH.

2 WHO. 2015. *Global Action Plan on Antimicrobial Resistance.* Geneva. https://apps.who.int/iris/handle/10665/193736

elements within those legal instruments, becomes a crucial first step to begin utilizing legislation as an effective tool in the fight against AMR. Subsequently, sector specific legislation can set out explicit rules regarding prudent antimicrobial use, for example through laws governing veterinary medicinal products, pesticides and food safety. Furthermore, minimizing the need for antimicrobial use in agriculture can be affected through robust legislation for animal health and plant health. Finally, natural resources legislation provides a number of mechanisms through which environmental dispersal of antimicrobials can be limited.

It is hoped that this Legislative Study will support lawmakers in carrying out assessments of their legislative frameworks to determine the gaps, overlaps and inconsistencies within those frameworks, and will help these regulators find appropriate solutions to their particular challenges. This Study may also serve as a contextual, detailed and illustrative complement to the *Quadripartite One Health Legislative Assessment Tool for Antimicrobial Resistance*.[3]

3 FAO, UNEP, WHO and WOAH. (forthcoming). *Quadripartite One Health Legislative Assessment tool for Antimicrobial Resistance*.

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Abbreviations

AAHC	WOAH Aquatic Animal Health Code
AB	Appellate body
ADI	Acceptable daily intake
AMC	Antimicrobial consumption
AMCRA	Antimicrobial consumption and resistance in animals
AMR	Antimicrobial resistance
AMU	Antimicrobial use
API	Active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
CAC	Codex Alimentarius Commission
CBD	Convention on Biological Diversity
COVID-19	Coronavirus disease 2019
DAFM	Department of Agriculture, Food and the Marine (Ireland)
EC	European Communities
ECOWAS	Economic Community of West African States
EIA	Environmental impact assessment
ESIA	Environmental and social impact assessment
FAO	Food and Agriculture Organization of the United Nations
FBO	Food business operator
GAP	Good agricultural practice
GDP	Gross domestic product
GHP	Good hygiene practice
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GLP	Good laboratory practice
GMP	Good manufacturing practice
HACCP	Hazard analysis and critical control points

HPCIA	Highest priority critically important antimicrobials
HPRA	Health Products Regulatory Authority (Ireland)
IACG	UN Interagency Coordination Group on AMR
ICCPM	International Code of Conduct on Pesticide Management
ICH	International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use
IPM	Integrated pest management
IPPC	International Plant Protection Convention
IPR	Intellectual property right
ISPM	International Standards for Phytosanitary Measures
MEA	Multilateral environment agreement
MERCOSUR	Southern Common Market trading bloc of South America
MoU	Memorandum of Understanding
MRL	Maximum residue limit
NAP	National action plan
NDC	Nationally determined contributions
NGO	Non-governmental organization
OECD	Organisation for Economic Co-operation and Development
OHHLEP	One Health High Level Expert Panel
OIE	Office International des Epizooties (now WOAH)
PIC	Prior informed consent
RIA	Regulatory impact assessment
RMR	Risk management recommendations
SADC	South African Development Community
SDG	Sustainable Development Goal
SPS	Sanitary and phytosanitary measures
SPS Agreement	World Trade Organization Agreement for the Application of Sanitary and Phytosanitary Measures
TAHC	WOAH Terrestrial Animal Health Code

TBT Agreement	WTO Agreement on Technical Barriers to Trade
TFDA	Tanzania's Food Drugs and Cosmetics Act
TRIPS Agreement	Agreement on Trade-Related Aspects of Intellectual Property Rights
UNCLOS	United Nations Convention on the Law of the Sea
UNEA	United Nations Environment Assembly
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environment Programme
UNGA	General Assembly of the United Nations
UNIDO	United Nations Industrial Development Organization
US-EPA	United States Environmental Protection Agency
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary medicinal product
VSB	Veterinary statutory body
WHO	World Health Organization
WOAH	World Organisation for Animal Health
WTO	World Trade Organization

1. Introduction

1.1. Antimicrobial resistance: causes and impacts

Antimicrobial resistance (AMR) refers to the ability of microorganisms – bacteria, fungi, viruses, and parasites – to persist or grow in the presence of an antimicrobial agent designed to inhibit or kill them (FAO, 2022a). In this Study, antimicrobial is the overarching name used for antibiotics (that work against bacteria), antivirals (against viruses), anti-fungals (against fungi) and anti-parasitics (against parasites). 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 CXG 77-2011, p. 5). An antimicrobial agent, on the other hand, 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 CXG 77-2011, p. 4). The definition of an antimicrobial agent adopted by the WOAH is largely the same, but it explicitly excludes anthelmintics and substances classed as disinfectants and antiseptics from its definition (WOAH, 2022).

Antimicrobials have a range of uses in the agriculture sector. Antimicrobials are used to treat sick animals, but also to promote growth and to prevent disease in healthy ones. Antimicrobials are used in aquaculture activities, as well as for crop production and plant health. While occurring naturally through microbial adaptation to the surrounding environment, AMR has been exacerbated by misuse and overuse in the agriculture sector (as well as in the human health sector). Microorganisms are becoming resistant to the antimicrobials to which they were previously susceptible. This heightens the risk of rendering inefficacious the antimicrobials that are reserved for the treatment of life-threatening infections in humans. Furthermore, with few exceptions, the same antimicrobial classes are used in human medicines and veterinary medicinal products (VMPs) (Codex CXG 77-2011) and in some cases also the same as plant protection products. This further threatens the efficacy of antimicrobials available to treat infections and diseases in both humans and animals, but especially those considered critically important for human health, and which are used as the last resort in the most serious and difficult cases. Indirect human exposure to AMR results from the prevalence and persistence of antimicrobials (and their residues and metabolites) as well as the development and spread of antimicrobial-resistant microorganisms and genes in the environment. These risks are added to the potential risks from the spread of resistant microorganisms and genes from animals to humans, and via consumption of contaminated crops, foods of animal origin (FAO, 2020a), and through insufficiently treated wastewater.

Up to 80 percent of antimicrobials administered to humans or animals can be excreted in faeces and urine while still in an active form (FAO and WHO, 2019). Furthermore, surface runoff from farms which apply antimicrobials as pesticides or manure as fertilizer, results in the spread of antimicrobials and antimicrobial-resistant microorganisms and genes into neighbouring areas and nearby surface and groundwater bodies. Where wastewater treatment technologies are insufficient to remove all antimicrobial compounds, these agents and microorganisms can spread to multiple aquatic habitats, affecting humans that consume water from these sources as well as agriculture and aquaculture activities that rely on these sources. Antimicrobials can be released into the environment at different stages in the antimicrobial supply chain starting from manufacturing until final disposal and consumption either by humans or animals (ReAct, 2019).

In addition to direct impacts on human health, AMR threatens agricultural production, food security, and associated livelihoods (e.g. farmers and other actors in the food value chain). Furthermore, AMR impacts sustainable development (and specifically the 2030 Agenda for Sustainable Development) owing to its

wide-ranging impacts on human health, animal health, the environment and economic development. In the agriculture sector, the advances in veterinary medicine, as well as the social and economic shifts that have enabled widespread access to efficacious, quality and affordable VMPs, risk being eroded. The spread of AMR may result in increased incidence, prevalence and morbidity of animal diseases and pest outbreaks, thus damaging agricultural and natural resources and the services they provide and may also inhibit agricultural trade.

The economic consequences of AMR are significant – either because of the loss of livelihoods or owing to the increased severity of disease in humans, animals and plants. Data from the European Union suggests that the economic costs of healthcare and loss of productivity amount to EUR 1.5 billion per year in this region alone (European Commission, 2020). According to the World Bank, annual global gross domestic product (GDP) would likely fall between 1.1 percent and 3.3 percent by 2050, translating to an annual GDP shortfall of between USD 1 trillion and USD 3.4 trillion after 2030 (World Bank, 2017). In addition, dealing with AMR will require increased investments into new drugs and diagnostic capabilities as well as other interventions (ReAct, 2019). By 2030, 24 million people from least developed countries may be pushed into extreme poverty because of AMR, with concomitant effects on hunger and malnutrition (FAO, 2018).

The likelihood that new antimicrobials will outpace the spread of resistant microorganisms is shrinking. Meeting the challenge of preserving antimicrobial efficacy while still producing adequate safe food presents a major challenge for the food and agriculture sector. When understood that resistance to antimicrobials is occurring globally, across a range of microorganisms, the scale of the problem implies potentially catastrophic consequences. Resistance in one microorganism may spread rapidly through the exchange of genetic material between different microorganisms to different locations (WHO, 2015). The Political Declaration of the High-level Meeting on Antimicrobial Resistance (A/RES/71/3) stated in 2016 that resistant microorganisms can circulate in both human and animal populations, and spread through food, water and the environment; and transmission may be heightened by trade, travel and both human and animal migration. In the case of antibiotics for example, resistance to one antibiotic agent may result in resistance to an entire related class of antibiotics. While innovation plays an important and critical role, the global scale of the AMR problem requires multiple-pronged action, including ensuring that the regulatory framework responds to key risks and challenges with effective country-specific solutions.

Likely due to the concerted effort of stakeholders in recent years, WOAH announced a decline by 27 percent in the use of antimicrobials for animals (WOAH, 2022). Where regulatory efforts gather momentum, results will be evident at national and global levels. Notwithstanding, the development, transmission and spread of AMR remains a complex and evolving challenge that spans a number of sectors. Any regulatory response to AMR must be intersectoral, rooted in a One Health approach, not only in understanding the causes and impacts, but also in the design of solutions specific to each country context and need.

1.2. Antimicrobial resistance and One Health

The threat of AMR, as well as the Coronavirus Disease 2019 (COVID-19) pandemic and other emerging infectious diseases, remind the world of the linkages between human, animal and environmental health, and underline the urgent need to address these risks and challenges in a holistic manner. One Health (see Box 1 for a definition), is now well-established in the global agenda, including the G7, G20 and the UN Food Systems Summit (2021), as a sustainable approach to health risks. Specifically, AMR has been described as the "quintessential One Health issue" (Robinson *et al*., 2016, p. 1) owing to its clear links to human, animal and environmental health. This has also been recognized by the UN General Assembly (UNGA) in its *Resolution A/RES/73/132*, which states the "global challenge of antimicrobial resistance, … requires multisectoral actions, through the One Health approach". The Codex Alimentarius Commission

(CAC) frames the One Health approach as a "collaborative, multisectoral, and trans-disciplinary approach working with the goal of achieving optimal health outcomes recognizing the interconnection between humans, animals, plants/crops, and their shared environment" (Codex Alimentarius, CXC 61-2005, p. 4).

Box 1. Definition of One Health

One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of humans, animals and ecosystems. It recognizes that the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and interdependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, clean energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development.

Source: FAO, OIE, WHO & UNEP. 2021. Joint Tripartite (FAO, OIE, WHO) and UNEP Statement - Tripartite and UNEP support OHHLEP's definition of "One Health". https://www.fao.org/3/cb7869en/cb7869en.pdf

The One Health paradigm embraces interdisciplinary collaboration and communication, and involves embedding the tenets of gender equality and economic and social responsibility in the approach. Legislation is one tool to implement the One Health approach through an enforceable framework that is characterized by multisectoral cooperation and coordination. While this Study does not encompass the legislative frameworks for human health, the legislative frameworks examined in Section 6 to Section 8 on the food and agriculture sector emphasize the importance of adopting a multisectoral view when analysing relevant legislation in line with a One Health approach.

1.3. Role of legislation in addressing antimicrobial resistance

Legislation[4] creates a clear framework of reference for all actors and provides for principles and mechanisms that can contribute to reduced and mitigated AMR. A robust policy and institutional structure that is underpinned and implemented by sound legislation is essential to meet the challenges posed by AMR. The ultimate goal of legislation in addressing AMR should be to improve agricultural productivity while avoiding the risks of AMR arising from the improper use of antimicrobials (FAO, 2020a). Laws relevant to AMR may establish provisions for controlling the use of antimicrobials, for mitigating the risks of the development and spread of AMR, but also for reducing the need for antimicrobials in the first place. Legal frameworks for agriculture systems, including laws on production and health, should embrace the social, economic and environmental aspects relating to the reduction of disease risk, preventing the unnecessary use of antimicrobials, adopting good animal husbandry management and strengthening biosecurity measures (FAO, 2016).

Regulators should be aware that not all issues should be addressed through legislation; some challenges may be better addressed through non-legislative means, such as codes of practice or awareness-raising campaigns. Legislation establishes controls within a sector, establishes linkages among different sectors, and facilitates collaboration by multiple competent authorities. Good legislation thus contributes to institutional frameworks that are coordinated and effective; a critical feature of regulatory frameworks to address AMR.

4 The term 'legislation' in this Study refers to primary and secondary legislation such as laws, acts, regulations, ordinances and decrees. Where law is used with a lower case 'l', it is used to refer to legislation in a generic and broad manner, no matter the level or type.

Countries may use existing legislation as is, or where required, may amend it or adopt new legislation to address AMR challenges. The various legal instruments that are relevant to address AMR are not necessarily designed to address AMR specifically. A specific reference to AMR or antimicrobials is not necessarily needed to utilize a particular provision for the purposes of addressing AMR. For instance, a water law that gives the competent authority capacity to approve, monitor and control water quality requirements will be sufficient for such government to introduce AMR-related considerations in water management, even in the absence of explicit references to AMR. Therefore, the focus in this Study is on key tools and mechanisms that can be leveraged to address an AMR risk. Legislation in different sectors (veterinary matters, pesticides, environment, food safety, etc.) may contain the appropriate tools already, i.e. restrictions and prohibitions or licences and inspections.

In deciding on whether to legislate or not, the primary consideration is whether the required policy imperative, implementation goal, or behavioural change warrants foundation in a legal instrument. Regarding the amendment of existing laws or the adoption of new laws, it should be noted that the multisectoral and multidisciplinary nature of AMR, as well as the rapidly evolving technical and policy base, make setting regulatory agendas for reform challenging. The dynamic nature of scientific understanding and developments in this area means that regulatory frameworks (the development of which is typically protracted in many countries) must be flexible enough to implement changing technical parameters.

1.4. Objectives of this Study

The UN General Assembly has called for "strengthening of regulatory capacity" as well as efforts to "increase awareness and knowledge, and [share] good practices and findings" in the global fight against AMR (UNGA, 2016, p. 4). This Study seeks to contribute to both those goals.

This Study is designed to demonstrate the various ways in which key AMR risks and challenges can be tackled through legislation. The subsequent sections outline concepts and mechanisms relevant to address AMR for the twin goals of attaining responsible and prudent use of antimicrobials and the mitigation of AMR. Where available, national legislations are offered as examples. This Study may serve as a detailed complement to the chapters on food and agriculture of the *Quadripartite One Health Legislative Assessment Tool for Antimicrobial Resistance* (forthcoming). The assessment tool sets out a simplified but specific framework to enable countries to pinpoint gaps and weaknesses and to *assess* overall the adequacy of their legislative frameworks to respond to AMR. This Study sets out more broadly the various elements of relevant regulatory mechanisms and tools. It also outlines the factors to be taken into consideration when designing or selecting regulatory mechanisms, and in its comparative approach, it may serve as a useful complement to both legislative assessment and legislative reform/revision activities.

1.5. Scope and approach of this Study

Approach

This Study identifies the relevant regulatory areas and extracts the key elements within these areas that are necessary to effectively address AMR challenges. For each regulatory area identified, the corresponding section will demonstrate its linkage to AMR, and set out the key elements or provisions that should feature in legislation. International standards and good practices are used as benchmarks for these elements/provisions. However, the sections of this Study are not intended to serve as comprehensive guides to regulation of the sectors as a whole – only aspects that are *relevant to AMR* are canvassed in this Study.

Guidance for comprehensive regulation of each of the sectors is available in reference materials and publications elsewhere.[5] Direct citations of international standards provide current and updated wording as of August 2022.

For ease of identifying the regulatory areas that might have an impact on AMR and to facilitate discussions, this Study differentiates between: (a) legislation that directly regulates antimicrobials in food and agriculture; (b) legislation that deals with exposure of humans to antimicrobials as well as antimicrobial resistant microorganisms and genes through the environment and through food; (c) legislation that ultimately reduces the need for antimicrobial use; and (d) legislation that makes specific provisions for AMR governance or institutional arrangements or that otherwise addresses specific AMR integrated mechanisms, such as integrated surveillance.

As regards category "(a)" above, legislation that governs the prudent use of antimicrobials and that regulates the quality, safety and efficacy of antimicrobials is given primacy due to its direct nexus with AMR development. This includes antimicrobials for animal health (e.g. VMPs) as well as antimicrobials used in feed and for crop production (e.g. pesticides). These types of laws provide a framework for antimicrobials at all stages of their lifecycle, from production to disposal, including procurement, registration, placement on the market, transport, sale and use. Countries may have comprehensive legislation governing these different stages or may have different laws that deal with, for example, the authorization and use of antimicrobials separate from disposal and waste management.

The "(b)" category looks at the ways in which legislation prevents contamination of food and the environment with antimicrobials and antimicrobial residues. Legislation for food control systems can help minimize and control the presence of residues in food products, for e.g. through the regulation of maximum residue limits (MRLs). The environmental development and spread of AMR can be contained using provisions relating to pollution control, the establishment of quality standards for soil and water, and wastewater management, among other selected environmental law mechanisms.

The "(c)" category looks at legislation that seeks to protect animal health and plant health (and disease resilience) and thus *minimize* the need for antimicrobials. These are largely found in laws that govern plant health and animal health, including trade-related texts focusing on sanitary and phytosanitary matters. These laws contain mechanisms geared towards preventing health risks, and for controlling the occurrence and spread of pests and diseases. Also discussed in this Study, is legislation governing a country's veterinary services, including veterinarians and veterinary paraprofessionals and their role in dispensing antimicrobials. Any legislation regulating agricultural production practices and mechanisms that reduce the need for antimicrobials, such as integrated pest management (IPM) would also be relevant for analysis (see Section 7.3.3 of this Study).

The final category under "(d)" looks at legislation for the governance of AMR and integrated regulatory solutions. While the other three categories have been used to structure this Study to enable an understanding of the legislation *relevant for* AMR, it should be emphasized that some countries have promulgated legislation *specific to* AMR. It is the view of the authors that AMR-specific laws, except for those that set out specific arrangements for coordination or management of AMR at national level, can quite often create more problems than they resolve. Such laws include those that are broad in scope and that capture the entire AMR phenomena across multiple sectors and thus regulate various aspects of those sectors, or laws with a narrower scope focusing on a specific aspect of the AMR challenge for the country (again treating a specific regulatory area in isolation). A legislative response to AMR should always be a context-specific exercise. The risk with some AMR-specific laws that do not focus on bringing existing legislation or institutions together is that they risk legal fragmentation, duplication or inconsistency.

5 See the publications by the FAO Legal Office: https://fao.org/legal-services/publications/legislative-studies/en/

Subject matter scope

This Study focuses on AMR from the perspective of the agriculture sector. While the Study is aligned with the One Health approach, aside from food safety and environmental dimensions, other regulatory aspects relating to public (human) health are not included (that are not directly relevant or related to the food and agriculture sectors, such as the regulation of human medicines or hospitals).

In this Study, a broad interpretation of "agriculture" is used to mean all activities related to terrestrial and aquatic animal health and production, plant health and production, and forestry. The term "environment" is used to include all natural resources and includes agricultural, forestry and aquatic ecosystems, wildlife, biodiversity and other natural resources more broadly.

Illustrative boxes and legislative examples

The country examples are used for illustration purposes only and may or may not be applicable in other legal systems. It is possible that legislative provisions highlighted in this Study work well in design but are implemented poorly or have had negative consequences in practice. This Study does not address implementation of the law, rather, its purpose is to guide design of the legal framework to avoid common pitfalls in implementation.

Furthermore, the regulatory mechanisms highlighted here present only some of the options that can be adopted and adapted based on the specific needs of the country. Similarly, the boxes are used to highlight certain stories or legislation relating to AMR and are not intended as a one-size-fits-all or a blanket recommendation for application in all countries. Finally, it should be recalled that this Study captures current thinking and areas of research in a rapidly evolving policy space, and any recommendations or areas highlighted should be taken with that understanding.

2. Overview of international actions to address antimicrobial resistance

Owing to the global and pervasive nature of the AMR challenge, a number of global initiatives have been launched to spearhead country-level action. These are briefly canvassed below.

2.1. United Nations General Assembly Resolution A/RES/71/3

During the Seventy-First Session of the United Nations General Assembly (UNGA) on 21 September 2016, Member States adopted the *Political Declaration of the High-level Meeting on Antimicrobial Resistance (A/RES/71/3)*. This Resolution underscores the overarching principle for addressing AMR, which is the protection of human health under a One Health approach that recognizes the interconnection between the animal, human and environmental dimensions. This Resolution draws attention to the importance of safe, reliable and affordable antimicrobials when required, as well as the need for healthy food and environments. The Resolution notes the need for regulatory capacity for antimicrobials for humans and animals enforced "according to national contexts and consistent with international commitments" (p. 5). Importantly, sharing knowledge on AMR through the exchange of good practices and findings is promoted. Such awareness-raising activities include promoting "evidence-based prevention, infection control and sanitation programmes; the optimal use of antimicrobials in humans and animals; and appropriate prescriptions by health professionals" (p. 5), among other aspects. The Resolution also recognizes that relevant sectors of government should be engaged in the development and implementation of multisectoral NAPs, policies, regulations and regional initiatives, taking into account the national context, legislation and jurisdictional responsibilities.

2.2. Quadripartite collaboration

The FAO, WOAH and WHO collaboration launched in 2010, and was recognised as the Tripartite partnership. Upon the joining of UNEP in March 2022, this alliance became known as the Quadripartite partnership. This international-level arrangement emphasizes the sharing of responsibilities among the four organizations and the coordination of global initiatives to address health challenges at the human-animal-ecosystem interfaces. The partnership recognizes the importance of country efforts to improve their national legislation in the areas of "animal production, food safety, inspection and certification of animal products, importation or internal quality control of pharmaceuticals, as well as compliance with international obligations" (FAO, OIE and WHO, 2010, p. 4). The partnership also places emphasis on the One Health agenda, recalling that "the approach can be applied at community, subnational, national, regional, and global levels, and relies on shared and effective governance, communication, collaboration and coordination. With the One Health approach in place, it will be easier for people to better understand the co-benefits, risks, trade-offs and opportunities to advance equitable and holistic solutions" (FAO, OIE, WHO and UNEP, 2021, p. 2).

Global Action Plan on AMR

In 2015, the World Health Assembly adopted a *Global Action Plan on Antimicrobial Resistance*, which outlines specific recommendations to prevent and limit the spread of AMR. This Global Action Plan recommends (among a range of mechanisms), the elaboration of country-specific NAPs on AMR, underpinned by a One Health approach. The Global Action Plan also calls for NAPs to reflect several key principles, including: broad stakeholder engagement; prevention first (i.e. good sanitation, hygiene and other prevention measures that can slow the spread of infections); and equitable access to, and appropriate use of, antimicrobials. These key principles reflect the four categories of legislation reviewed in this Study. This global call to action establishes five strategic objectives which include: (i) improving awareness and understanding of AMR; (ii) strengthening knowledge through surveillance and research; (iii) reducing the incidence of infection; (iv) optimizing the use of antimicrobials; and (v) sustainable investment into new medicines, diagnostic tools, vaccines and other interventions (WHO, 2015).

FAO Action Plan on AMR

FAO has published *The FAO Action Plan on Antimicrobial Resistance 2021–2025*, which builds on the lessons learned from *The FAO Action Plan on Antimicrobial Resistance 2016-2020*. The Action Plan 2016–2020 focused on the food and agriculture sector and encompassed animal health and production (including terrestrial and aquatic animals), and crop production and food safety. The Action Plan 2021–2025, which primarily guides the organization's support to countries in tackling AMR, has heightened focus on controlling antimicrobial use as one of the main drivers to combat AMR. It also emphasizes the need to support awareness-raising activities, support stakeholder engagement and support targeted field interventions. The need for the sustainability of mechanisms that support AMR responses is also underscored. Efforts are focused around five objectives that align with the Global Action Plan on AMR with a strengthened focus on governance, these are: (i) increasing stakeholder awareness and engagement; (ii) strengthening surveillance and research; (iii) enabling good practices; (iv) promoting responsible use of antimicrobials; and (v) strengthening governance and allocating resources sustainably (FAO, 2021a). This Study contributes to efforts under the fifth outcome, which includes within its remit, support to countries' policy and regulatory frameworks to address AMR.

WOAH Strategy

The WOAH published *The OIE Strategy on Antimicrobial Resistance and the Prudent Use of Antimicrobials* in 2016, setting out WOAH's approach to address AMR in line with the Global Action Plan. Confirming the primacy of a One Health approach, the Strategy underscores the importance of international standards and the updating of national legislation covering registration/authorization, production, importation, distribution, prescription, use, surveillance, and general control of antimicrobials in veterinary medicine. The Strategy promotes the responsible and prudent use of antimicrobials by highlighting the importance of veterinary oversight and appropriate training of veterinarians and veterinary paraprofessionals, in addition to other good practices relating to sanitation, biosecurity to prevent disease, and good animal husbandry (WOAH, 2016).

UNEP initiatives

In 2017, the United Nations Environment Assembly (UNEA), the governing body of UNEP recognized AMR as an emerging issue of environmental concern, and a threat to global health, food security and sustainable development. The UNEA underscored the risk to biodiversity and ecosystems arising from anthropogenic AMR in the environment, and fully endorsed the One Health approach. The UNEA called for the specific examination of environmental impacts of AMR and the causes for its development and spread in the

environment, including gaps in the understanding of those impacts and causes (UNEP, 2017). In 2018, FAO, WHO and WOAH signed a Memorandum of Understanding (MoU) with UNEP, signalling the start of a Quadripartite cooperation to better integrate the environmental dimension in addressing AMR.

The ad-hoc Interagency Coordination Group on AMR and global AMR governance

In 2016, the UNGA under Resolution A/RES/71/3 called upon FAO, WOAH and WHO to finalize a global development and stewardship framework to support the control, distribution and use of antimicrobials, taking into account the needs of all countries and in line with the Global Action Plan. A 2018 draft roadmap document (developed also with UNEP), outlines the following as some of the main objectives: (i) supporting affordable diagnostics, treatments and alternatives to antimicrobials; (ii) filling knowledge gaps, particularly in the environment sector; (iii) establishing sustainable global multisectoral governance to coordinate action to combat AMR with an accountability framework; and (iv) ensuring that all relevant stakeholders are included in the collective action.

On the basis of Resolution A/RES/71/3 paragraph 15, the UN Secretary General established an ad hoc Interagency Coordination Group (IACG) on Antimicrobial Resistance to provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance, including options to improve coordination. An IACG report in 2019 recommended the establishment of a One Health Global Leadership Group on Antimicrobial Resistance, supported by a Joint Secretariat managed by FAO, WOAH and WHO. It also recommended convening an Independent Panel on Evidence for Action against Antimicrobial Resistance in a One Health context to monitor and provide Member States with regular reports on the science and evidence related to AMR. It further called for the systematic and meaningful engagement of civil society groups and organizations and the private sector – all as stakeholders in the One Health response to AMR at global, regional, national and local levels (IACG, 2019). The report includes various recommendations of a regulatory nature to be implemented, such as the need for "strengthening and maintaining national regulatory and accountability mechanisms and monitoring and surveillance systems" at the national level (IAGC, 2019, p. 10); and at the global level, the need for harmonized regulatory guidance for the registration and commercialization of antimicrobials and alternatives to antimicrobials.

The Global Leaders Group, established in November 2020, provides guidance on six priority areas of work which include: sustained political action; transformation of human, animal, plant health and food safety, and environmental ecosystems; improved surveillance and monitoring; financial resources; increased innovations; and better understanding of environmental pathways to the development of AMR. The AMR Multistakeholders Partnership Platform was launched in Rome on 15 November 2023. The Platform aims to catalyse a global movement for action against AMR by fostering cooperation between stakeholders at all levels of the One Health spectrum.

2.3. Sustainable Development Goals and antimicrobial resistance

Addressing AMR is also seen as one of the challenges to be undertaken under the Sustainable Development Goals (SDG) framework. To this end, AMR is mentioned in paragraph 26 of the Preamble to the SDGs in the *2030 Agenda for Sustainable Development*. The development and spread of AMR create particularly relevant risks for the achievement of at least six SDGs: SDG 2 (Zero Hunger), SDG 3 (Good Health and Well-being), SDG 6 (Clean Water and Sanitation), SDG 9 (Industry, Innovation and Infrastructure), SDG 12 (Responsible Consumption and Production), and SDG 17 (Partnerships for the Goals). Furthermore, SDG indicators indirectly cover many aspects of AMR, with 90 indicators across 12 SDGs found to be relevant

for AMR (Welcome Trust, 2018). For example, under SDG 3 on Good Health and Well-being, Indicator 3.d.2 refers to the "Percentage of bloodstream infections due to selected antimicrobial-resistant organisms".

Specifically, Goal 2 (Zero Hunger) is impacted on multiple fronts. The manner in which antimicrobials are used in agriculture threatens food production, creates food safety hazards, and puts the livelihood of those dependent on the agriculture sector at risk. Industrial production of animals may lead to a higher use of antimicrobials; the increasing demand for animal products further drives this trend. In addition, SDG 6 (Clean Water and Sanitation) is directly impacted, as untreated wastewater and water bodies that have been polluted with antimicrobials are reintroduced into the water supply for human consumption as well as for agricultural activities.

One of the key recommendations in the IACG report (2019) was for countries to accelerate the development and implementation of One Health NAPs on AMR within the context of the SDGs. The report also noted that while AMR is not specifically mentioned in the SDG targets, AMR is recognized in the *Global Action Plan for Healthy Lives and Well-being for All* as a barrier to achievement of SDG 3 on human health. The report further noted that AMR directly jeopardizes progress against other SDGs related to food security (SDG 2), clean water and sanitation (SDG 6), and responsible consumption and production (SDG 12). Also, AMR was recognized as having negative cascading effects, for example, hampering economic development and increasing inequality, and as such indirectly threatening progress against SDGs that aim to reduce poverty (SDG 1) and inequality (SDG 10). Overall, the IACG considers that the SDGs cannot be achieved if AMR is not addressed with greater urgency (IACG, 2019).

3. International regulatory framework relevant for antimicrobial resistance

3.1. Trade and the Agreement for the Application of Sanitary and Phytosanitary Measures

Antimicrobials are used against diseases in the production of terrestrial and aquatic animals and used for crops and wild plants against plant pests. Agricultural products are subject to a range of sanitary and phytosanitary (SPS) measures both in the domestic context (explored in Chapter 9) and when traded internationally. Two key issues are raised in the context of international trade governing agricultural products. First, antimicrobials that are misused or overused will be ineffective against pests and diseases, creating an increased sanitary or phytosanitary risk, making it harder to produce goods that meet sanitary standards and requirements for international trade. Second, where the agricultural commodities imported or exported are food for human consumption, additional concerns relate to antimicrobial residues on the food products, as well as the spread of antimicrobial-resistant microorganisms and genes.

These matters fall within the scope of the World Trade Organization *Agreement for the Application of Sanitary and Phytosanitary Measures (SPS Agreement)*. The SPS Agreement is a legally binding international instrument for all WTO members (i.e. Member States must comply with it through their national legislation). The Agreement sets out key principles to guide measures for food safety, animal health and plant health applied to internationally traded goods, and also circumscribes the rights of Member States to take health measures on imports in order to facilitate trade. While the SPS Agreement targets measures applied to imports of SPS-sensitive goods into a country, logically, exports from the country of origin (or third country) should be compliant with the SPS requirements of the importing country, in order to gain access to its market.

Annex A of the Agreement defines SPS measures to mean those taken to protect against risks arising from:

a. pests, diseases and disease-carrying or disease-causing organisms – these affect animal and plant life and health, and in the case of diseases, human health as well, and are thus relevant for AMR.

b. additives, contaminants, toxins or disease organisms in food, drink and feedstuffs – these affect human and animal health and are thus relevant for AMR.

c. other damage caused by the entry, establishment or spread of pests and diseases in the territory of a Member – this generally refers to environmental or economic damage.

Though the focus of this Study is on legislation, the term "measures" in the SPS Agreement includes "all relevant laws, decrees, regulations, requirements and procedures" taken by a state in order to protect human health, animal health and plant health, and to prevent the spread of diseases and pests (Annex A of the SPS Agreement). According to the Agreement, Member States have the right to set out such measures at their appropriate level of protection, but such measures should not be more trade-restrictive than necessary. Full implementation of the disciplines of the SPS Agreement, through national SPS legislation and its effective implementation, is still a work in progress in many countries.

According to the principle of scientific justification, SPS measures must: be based on scientific principles; be applied only to the extent necessary to protect human, animal or plant life or health; not be maintained without sufficient scientific evidence; and be based on international standards or risk assessment (Article 2, 3 and 5 of the SPS Agreement). Member States are encouraged to harmonize their measures with international standards, guidelines or recommendations (Article 3) and to recognize as equivalent the measures taken by an export trading partner that achieves the level of protection required by the importing country (Article 4). A measure must be necessary to achieve the objective and should be proportional to the risk.

To prevent SPS measures from becoming disguised restrictions on trade, and in furtherance of the principle of harmonization, the SPS Agreement encourages governments to establish national SPS measures consistent with the standards, guidelines and recommendations of the three international standard-setting bodies. These bodies are the International Plant Protection Convention (IPPC) (see Section 3.4 of this Study), Codex Alimentarius Commission (CAC) (see Section 3.2 of this Study), and the World Organisation for Animal Health (WOAH) (see Section 3.3 of this Study). Where an SPS measure is based on the international standards, guidelines or recommendations of these bodies, the measure is presumed to be science-based and WTO-consistent, unless demonstrated otherwise. Countries may opt against using international standards if they can provide technical or scientific justification that the measure is necessary to achieve their desired level of sanitary protection.

The principle of transparency requires that Member States establish an Enquiry Point and designate a Notification Authority. A notification of draft regulations, whether introducing new provisions or making changes to existing regulations, is required when no international standard exists, or where the new regulation has a significant impact on trade and is different to the international standard. A 60-day notice period is required for the latter notifications, which can be waived in the case of emergencies. Member States should also publish all SPS measures. Finally, SPS measures may be adopted on a provisional basis when relevant scientific information is insufficient. In such circumstances, Member States shall seek to obtain additional information to assess risk and must review the measure within a reasonable time.

Food safety or animal health measures for mitigating AMR that result in restrictions to trade might be challenged against SPS rules. Under the WTO Dispute Settlement Procedure, Member States that are unable to reach a mutually acceptable solution to a dispute arising under the SPS Agreement may have recourse to a body that is set up to hear the dispute. To date, no case has been filed under this WTO dispute procedure that involves AMR or antimicrobial use (AMU), but the *EC-Hormones case* provides an example of how a trade restriction based on international food standards operates. In this case, the disputed measure was the European Union's prohibition of the placing on the market (and the import) of meat and meat products treated with hormones for growth purposes. Box 2 offers a summary of this case.

Box 2. European Communities – Measures Concerning Meat and Meat Products (EC-Hormones case)

Complainants: **United States, Canada**
Respondents: **European Communities**

This case was considered by an appointed Panel and by the Appellate Body (AB). The AB found that SPS measures should be "based on" international standards, guidelines or recommendations for the purposes of harmonization, not necessarily to "conform to" such standards. Specifically, the AB found that the European Communities measure did not violate Article 5.5 by discriminating or being a disguised restriction on trade given that there were genuine anxieties concerning the safety of the hormones. Furthermore, it was considered that "harmonizing measures" was designed towards establishing a common internal market for beef.

The European Union and the United States of America signed a revised Memorandum of Understanding in 2013 regarding the details of the case.

Source: WTO. 2019. *European Communities – Measures Concerning Meat and Meat Products*. (DS26, 48). Geneva, Switzerland.

3.2. Codex Alimentarius Commission food safety standards

The CAC establishes standards, guidelines and codes of practice for the safety, quality and fairness of international food trade. As such, these references may serve as a basis for the development of national legislation for food safety (FAO and WHO, 2023a). From 2007 to 2011, the CAC established an ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance to address foodborne AMR. In 2017, the Task Force was re-established to develop science-based guidance on the management of foodborne AMR (FAO and WHO, 2017). The Codex texts specific to foodborne AMR include: *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance (CXC 61-2005)*; *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CXG 77-2011*); and the *Guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance (CXG 94-2021)*. In addition, the Codex texts relevant to foodborne AMR, include MRLs for veterinary drugs (FAO and WHO, 2020a) and for pesticides (FAO and WHO, 2020b).

The *Codex Alimentarius* defines food as "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" (FAO and WHO, 2023b, p. 23). This definition is relevant when considering AMR risks associated with different aspects of the food continuum. The CAC considers risk analysis a critical mechanism to determine the risk to public health from foodborne antimicrobial-resistant microorganisms. Appropriate response strategies should take into account both the biological complexity of AMR, and the multidisciplinary aspects of AMR within the entire food production to consumption continuum (FAO and WHO, 2008).

The 2021 version of the *Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance (CXC 61-2005)* was approved following almost a five-year process of negotiations. This renewed 2021 version adopts a One Health and full food chain approach that takes into consideration both, animal and plant sourced food in all stages of their production chain, including the release of waste resulting from food production into the environment. Countries should implement this Code of Practice in conjunction with the new *Guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance (CXG 94-2021)*. These Guidelines recommend surveillance in animals, plants/crops and food to be integrated with monitoring AMR along the food chain and the food production environment and do not cover antimicrobials used as biocides including disinfectants. The Guidelines also provide cross-references to the WOAH *Terrestrial Animal Health Code* and the *Aquatic Animal Health Code* regarding surveillance and data collection and reporting in food-producing animals. Similarly, the WOAH Health Codes also reference the Codex guidelines and recommendations relating to AMR (WOAH, 2023).

The CAC recommends the MRL for veterinary drugs (or VMPs) that is legally permitted in food, as compiled in the Commission's *Maximum Residue Limits (MRLs) and Risk Management Recommendations (RMRs) for Residues of Veterinary Drugs in Foods*. The MRL for a VMP 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. The MRL for a VMP also takes into account other relevant public health risks as well as food technological aspects. When establishing an MRL for a VMP, consideration is also given to residues that occur in food of plant origin that are sourced from the environment. The MRL may be reduced to be consistent with good practices in the use of these drugs and to the extent that practical analytical methods are available. These MRLs for VMPs are defined as the maximum concentration of residue resulting from the use of a VMP (expressed in mg/kg or μg/kg on a fresh weight basis) (FAO and WHO, 2018).

The MRL for pesticides has been defined by the CAC as the "maximum concentration of a pesticide residue (expressed as mg/kg), recommended by the [CAC] to be legally permitted in or on food commodities and animal feeds" (Pesticide Database Glossary, Codex Alimentarius). The MRLs are based on data from *Good Agricultural Practice in the Use of Pesticides*. Foods derived from commodities that comply with their respective MRLs are considered to be toxicologically acceptable. Codex MRLs, which are primarily envisioned towards international trade, are derived from estimations made by the annual Joint FAO/WHO Meeting on Pesticide Residues following: (i) a toxicological assessment of the pesticide and its residue; and (ii) review of residue data from supervised trials, and supervised uses including those reflecting national food agricultural practices. 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 (FAO and WHO, 2020c).

3.3. World Organisation for Animal Health standards

The WOAH *Terrestrial Animal Health Code (TAHC)* and *Aquatic Animal Health Code (AAHC)* cover animal health, animal welfare, and veterinary public health (WOAH, 2023).

Relevant standards addressing AMR in the TAHC include Section 3, Chapter 3.4 on veterinary legislation, particularly Article 3.4.9 on animal diseases and Article 3.4.11 on veterinary medicines and biologicals. Also, Section 6 on Veterinary Public Health contains several chapters on AMR. In the AAHC, Section 6 also includes multiple chapters that specifically address antimicrobial use in aquatic animals.

The following paragraphs outline the key elements of the specific provisions of Section 6 of the respective Codes that deal specifically with AMR. In particular, Chapter 6.10 of the TAHC contains extensive detail on the responsible and prudent use of antimicrobials in veterinary medicine (see Box 3), defining the respective responsibilities of the competent authority and all relevant stakeholders.

Box 3. Summary extracts of Section 6, Chapter 6.10 of the WOAH Terrestrial Animal Health Code

Article 6.10.3. Responsibilities of the Competent Authority

1. Marketing authorisation.
2. Quality control of antimicrobial agents and veterinary medicinal products (VMP) containing antimicrobial agents.
3. Assessment of therapeutic efficacy.
4. Assessment of the potential of antimicrobial agents to select for resistance.
5. Establishment of acceptable daily intake, maximum residue limit (MRL) and withdrawal periods in food-producing animals.
6. Protection of the environment.
7. Establishment of a summary of product characteristics for each VMP containing antimicrobial agents.
8. Post-marketing antimicrobial surveillance.
9. Supply and administration of the VMP containing antimicrobial agents.
10. Control of advertising.
11. Training on the usage of antimicrobial agents.
12. Research.

Article 6.10.4. Responsibilities of the veterinary pharmaceutical industry with regards to VMP containing antimicrobial agents

1. Marketing authorisation.
2. Marketing and export.
3. Advertising.
4. Training.
5. Research.

Article 6.10.5. Responsibilities of wholesale and retail distributors

1. Prescription requirements.
2. Record-keeping.
3. Training.

Article 6.10.6. Responsibilities of veterinarians

1. Use of antimicrobial agents.
2. Choosing antimicrobial agents.
3. Appropriate use of the VMP containing antimicrobial agents chosen.
4. Recording of data.
5. Labelling.
6. Training and continued professional development.

Article 6.10.7. Responsibilities of food animal producers

Article 6.10.8. Responsibilities of animal feed manufacturers

Source: WOAH. 2023. Codes and Manuals. In: WOAH - World Organisation for Animal Health. Cited 5 July 2023. https://www.woah.org/en/what-we-do/standards/codes-and-manuals

Surveillance is identified as a core pillar of the Global Action Plan on AMR (see Chapter 2 of this Study). In line with the Plan, Chapter 6.8 of the TAHC sets out provisions for the harmonization of AMR surveillance and monitoring programmes by setting out general aspects, such as the core components, targets and the purpose of such programmes. The Chapter details guidance on sampling strategies (including size of samples and sources), recording, storage and interpretation of data, reference laboratories, and annual reports. The Chapter reiterates that the objectives of surveillance are to determine the pattern and source of AMR, to provide data for risk analyses and for evaluating prescription practices, and to assess the effectiveness of strategies to combat AMR. With respect to aquatic animal health in the AAHC, the objectives of surveillance are to establish baseline data on the prevalence of antimicrobial-resistant microorganisms and determinants. Both Codes outline standards on monitoring quantities and usage patterns of antimicrobials used in food-producing animals and establish how to standardize antimicrobial monitoring systems.

3.4. International Plant Protection Convention and phytosanitary standards

The primary instrument governing plant health at international level is the *International Plant Protection Convention (IPPC)* adopted in 1951 and subsequently revised twice, in 1979 and in 1997. One of the chief objectives of this multilateral treaty is to secure "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" (Article 1). The IPPC outlines the obligations of signatory parties in relation to their phytosanitary systems and also provides a forum for international cooperation and technical exchange. The series of *International Standards for Phytosanitary Measures (ISPM)* approved by the Commission on Phytosanitary Measures (the governing body for the IPPC), provide guidance to countries on how to establish and operate phytosanitary systems, and how to identify, monitor and control pests both within their territories and in the context of international trade. While the obligations contained in the IPPC are legally binding, the ISPMs issued under the Convention are not binding *per se* but provide detailed guidance on the requirements articulated in the IPPC. Box 4 sets out a selection of ISPMs for illustration purposes, offering an overview of key areas and concepts relevant to this Study.

Phytosanitary measures and concepts enshrined in the IPPC that should be reflected in national phytosanitary laws include: pest risk analysis; the issuance of standardized phytosanitary certificates; surveillance; monitoring; and specific phytosanitary actions such as treatment, inspection, sampling, analysis etc. Pest risk analysis is essentially the backbone for phytosanitary regulation and must feature in plant health or phytosanitary legislation as such.

Box 4. Illustrative selection of International Standards for Phytosanitary Measures relevant to antimicrobial resistance	
ISPM 1	*Phytosanitary principles for the protection of plants and the application of phytosanitary measures in international trade (2006):* establishes core principles to reduce or eliminate the use of unjustifiable phytosanitary measures as barriers to trade.
ISPM 2	*Framework for pest risk analysis (1996):* describes the process of pest risk analysis to assist National Plant Protection Organizations in the preparation of phytosanitary regulations.
ISPM 4	*Requirements for the establishment of pest free areas (1996):* outlines the requirements for the establishment and use of pest free areas in connection with phytosanitary certification of plants and plant products for export.
ISPM 6	*Surveillance (1997):* describes the components of surveillance and monitoring systems for pest detection and for the provision of information for use in pest risk analysis, the establishment of pest free areas and the preparation of pest lists.
ISPM 7	*Phytosanitary certification system (1997):* describes the components of a national system for the issuance of phytosanitary certificates for export.
ISPM 8	*Determination of pest status in an area (1998):* describes the content of a pest record and outlines the use of pest records and other information in the determination of pest status in an area.
ISPM 9	*Guidelines for pest eradication programmes (1998):* describes the components of a pest eradication programme which can lead to the establishment or re-establishment of pest absence in an area.
ISPM 10	*Requirements for the establishment of pest free places of production and pest free production sites (1999):* describes requirements relating to these locations, similar to pest free areas.
ISPM 11	*Pest risk analysis for quarantine (2017):* provides details for conducting pest risk analysis to determine whether pests are quarantine pests.
ISPM 12	*Phytosanitary certificates (2001):* describes principles and guidelines for the preparation and issuance of phytosanitary certificates.
ISPM 16	*Regulated non-quarantine pests: concept and application (2002):* describes the concept of regulated non-quarantine pests and identifies their characteristics.
ISPM 17	*Pest reporting (2002):* describes the responsibilities of, and requirements for, contracting parties in reporting the occurrence, outbreak and spread of pests in areas for which they are responsible.
ISPM 19	*Guidelines on lists of regulated pests (2003):* describes the procedures for the preparation, maintenance and dissemination of national lists of regulated pests.
ISPM 20	*Guidelines for a phytosanitary import regulatory system (2004):* outlines the structure and operation of a phytosanitary import regulatory system.
ISPM 21	*Pest risk analysis for regulated non-quarantine pests (2004):* provides guidance for conducting pest risk analysis for regulated non-quarantine pests.
ISPM 22	*Requirements for the establishment of areas of low pest prevalence (2005):* outlines the procedures and requirements for the establishment of areas of low pest prevalence at national level.
ISPM 23	*Guidelines for inspection (2005):* describes the procedures for the inspection of consignments of plants and plant products and other regulated articles at import and export.

Source: Secretariat of the International Plant Protection Convention. 2023. Adopted Standards (ISPMs). In: *International Plant Protection Convention*. Cited 7 July 2023. https://www.ippc.int/en/core-activities/standards-setting/ispms

The Commission on Phytosanitary Measures

According to the IPPC Secretariat in 2021, to date there is no robust and definitive data on the extent and volume of antimicrobial use in the plant sector globally. There are regional and national differences in antibiotic recommendations, which may be a result of varying agricultural needs, diverse legislative requirements, availability of antimicrobials, varied cropping systems, extension services, or the nature of the pathogens that are causing problems. Some studies, however, have looked at the types of use for plant health. One such study found that at least 20 countries authorize antibiotic use to control fire blight and citrus greening disease in plants; in some countries, streptomycin is authorized to control certain bacterial diseases in pip fruit, stone fruit, seedling tomatoes and kiwifruit. Kasugamycin, oxytetracycline and oxolinic acid are other antibiotics used to control plant pests (de León *et al*., 2008; Stockwell and Duffy, 2012). Both the Commission on Phytosanitary Measures and its Strategic Planning Group have devoted attention to antimicrobial resistance and worked on identifying the interface between phytosanitary protection and AMR (FAO, 2021b, 2021c, 2022b).

3.5. Pesticides management

3.5.1. Code of Conduct

The International Code of Conduct on Pesticide Management (ICCPM) is a globally recognized non legally binding instrument that provides a pesticide management framework for all public and private entities engaged in, or associated with, production, regulation and management of pesticides. Pesticides are defined by the 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" (Article 2). This broad definition includes chemical and organic substances with antimicrobial effects. A central premise of the ICCPM is the lifecycle approach to managing pesticides, which entails the promotion of "practices which reduce risks throughout the lifecycle of pesticides, with the aim of minimizing adverse effects on humans, animals and the environment and preventing accidental poisoning resulting from handling, storage, transport, use or disposal, as well as from the presence of pesticide residues in food and feed" (FAO and WHO, 2014, Section 1.7.3).

The ICCPM is further accompanied by guidelines[6] to assist countries in implementing the terms of the Code at national level. These include *Guidelines for the Registration of Pesticides* (FAO and WHO, 2010) and *Guidance on Pesticide Legislation* (FAO and WHO, 2020b), as well as other guidelines that are useful for elaborating subsidiary legislation. While they do not impose legal obligations, in the interests of harmonization and adherence to international best practices, they are widely accepted as authoritative guidelines and used as benchmarks against which national legislation can be assessed and drafted.

3.5.2. Other instruments

There are legally binding texts relating to pesticides that address specific aspects of their lifecycle. Signatories to the *Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Pesticides and Industrial Chemicals in International Trade* commit to being bound by the Prior Informed Consent (PIC) procedure and information exchange mechanisms. Information exchange is primarily for the purposes of protecting health and the environment in chemicals trading. Two types of chemicals are eligible to be

6 For the complete list of guidelines: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/code/list-guide-new/en

"listed" in Annex III of the Rotterdam Convention and therefore are subject to the mandatory PIC procedure: "banned or severely restricted chemicals" (which include pesticides), and "severely hazardous pesticide formulations".

Other binding texts which must be considered when drafting national legislation include the *Stockholm Convention on Persistent Organic Pollutants*, the *Basel Convention on the Transboundary Movement of Hazardous Wastes and their Disposal*, and the International Labour Organization's *Safety and Health in Agriculture Convention (No. 184)* and the *Chemicals Convention (No. 170)*.

3.6. Fisheries-related instruments

The legally binding *United Nations Convention on the Law of the Sea (UNCLOS)* is the primary regulatory framework for the conservation and management of oceans and seas. It advocates ocean governance on the recognition that many challenges are interrelated. The UNCLOS exhorts contracting parties to regulate land-based sources of marine pollution (Article 213).

The *Code of Conduct for Responsible Fisheries* is a globally recognized non-legally binding instrument, although parts of it are based on relevant rules of international law (such as the UNCLOS). The Code establishes practices for the conservation, management and development of aquatic resources, and promotes the economic, social, environmental and cultural importance of the fisheries and aquaculture sectors. Section 9.1.5 of the Code stipulates that "States should establish effective procedures specific to aquaculture to undertake appropriate environmental assessment and monitoring with the aim of minimizing adverse ecological changes and related economic and social consequences resulting from water extraction, land use, discharge of effluents, use of drugs and chemicals, and other aquaculture activities" (FAO, 1995). The associated *FAO Technical Guidelines on Aquaculture Development* advocate the importance of environmental sustainability as a criterion for permits and licences. Related requirements may be in the form of a full environmental impact assessment (EIA) for projects that present a risk of environmental damage or – on the other end of the spectrum – a basic management and operational plan. Applicant aquaculture operators should be requested to submit data relating to escapes, diseases and other sources of negative environmental impacts (FAO, 2011).

3.7. Environment-related instruments

Multilateral environmental agreements (MEAs) form the overarching international legal basis for global efforts to address environmental issues. While the analysis of MEAs that are relevant for environmental protection are better addressed elsewhere, this section selects various themes and subject areas of relevance to AMR as a starting point and highlights key instruments that contain specific tools or mechanisms that would be useful for regulating AMR. Environment-focused legally binding and soft-law instruments are too numerous to list in meaningful detail here. For present purposes, it is sufficient to highlight that robust protections found in these instruments will help address the spread of antimicrobial-resistant microorganisms and genes in the natural environment.

Biodiversity

Biodiversity supports human health and sustainable development through goods and services that are sustained by well-functioning ecosystems. These goods and services (ecosystem services) are the benefits provided by natural resources and are diverse and broad in scope, from mitigating climate change, to the

pollination of crops by insects, to the filtration of water by trees. Notably, ecosystem services include the regulation of certain animal or plant diseases and can thus be seen as mechanisms to reduce the need for and use of antimicrobials in the first place.

The principal international text governing biodiversity, the *Convention on Biological Diversity (CBD)* has as its core objectives the conservation of biological diversity, the use of biodiversity components in a sustainable manner and the fair and equitable sharing of the benefits arising from the use of genetic resources. The CBD's vision of the *Strategic Plan for Biodiversity 2011-2020 (Decision X/2)* noted the linkages between biodiversity and human well-being and set out the *Aichi Biodiversity Targets*. Target 14 sets out – under a framework for enhancing benefits from biodiversity and ecosystem services – that ecosystems that provide essential services (including services related to water, and those that contribute to health, livelihoods, and well-being) are restored and safeguarded.

In *Decision XII/21 (2014)* on *Biodiversity and human health*, the governing body of the CBD recognized the value of the One Health approach as being consistent with the ecosystem approach, and integrating the network of linkages between humans, microorganisms, animals, plants, agriculture, wildlife, and the environment. The Decision also highlighted the importance of emphasis on preventive measures to strengthen the resilience of ecological systems, not only to mitigate health risks associated with loss of biodiversity, but also to protect the natural resource base from degradation resulting from human activities (e.g. deforestation, pollution, etc.).

The CBD's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) called for a more balanced integration of biodiversity and ecosystem dynamics in the 2017 document *Guidance on Integrating Biodiversity Considerations into One Health Approaches (CBD/SBSTTA/21/9)*. One of the measures promoted as a means to apply a One Health approach, is to align legislative frameworks with the principles set out in the Guidance. Thus, national legislative frameworks should "minimize or mitigate impacts of ecosystem alteration, waste, pollution, unsustainable use of resources, pharmaceuticals and antibiotics on ecosystem, animal, plant and human health" (Paragraph 23). The Guidance cites legislative mechanisms for these purposes as being for example: (i) the development of human activity or settlements away from biodiverse or sensitive ecosystems; and (ii) the reduction of environmental contamination with antimicrobials by adopting appropriate restrictions on antimicrobials to prevent their misuse and overuse. Furthermore, *Biodiversity and Health (SBSTTA 24/9)* issued in 2021, proposes a Draft Global Action Plan for Biodiversity and Health (see extracts in Box 5).

Box 5. Extracts of the Draft Global Action Plan for Biodiversity and Health (2021) relevant to antimicrobial resistance

Action area 1.1. Protect human, animal, plant and environmental health by promoting biodiversity and health linkages in the work and practices of Ministries, agencies and institutions responsible for biodiversity and health dimensions

Action area 1.2. Protect human, animal, plant and environmental health by promoting biodiversity and health linkages in the development and implementation of health, biodiversity, environment, forest and other related policies

1.2.3. Mainstream biodiversity considerations and biodiversity-health linkages in health policies, recognizing the importance of ecosystems for human health and animal welfare, including for the development of medicines, biotechnology and nutritious food;

1.2.5. Identify any unintended and undesirable negative impacts of biodiversity conservation measures on health, and of health interventions on biodiversity (e.g. risk of medicine residues in freshwater systems) and define specific entry-points to help evaluate, monitor and mitigate undesirable impacts

Action area 2.1. Mainstream biodiversity and health linkages through specific sectoral policies

2.1.3. Food systems

2.1.3.1. Enable a sustainable transformation of food systems, by leveraging agroecology, biodiversity and associated biodiversity for food and agriculture and the use of integrated pest management to reduce the need for chemical pesticides and herbicides;

2.1.3.2. Promote the diversity and sustainable use of wild foods, local crops and livestock, fisheries, including from marine and inland water sources, while ensuring the implementation of adequate sanitary controls for the consumption of wild meat;

2.1.3.3. With consideration of local characteristics, promote the use of effective tools and technologies, to contribute to sustainable production, food security and reduce the use of inappropriate antibiotics, pesticides and other chemical inputs;

Action area 2.3. Mainstream biodiversity in the health sector

2.3.3. Identify medicinal products with negative impacts on biodiversity, both for human and for veterinary uses, in order to target risk management, and avoid the overuse of antimicrobial agents in human medicine, veterinary practice, plant breeding and agricultural use;

2.3.4. Avoid the unsustainable use of threatened wild animals and plants for prescriptions for wherever possible, use alternative, sustainable sources for medicinal use;

2.3.5. Promote environmental surveillance through routine assessment including antimicrobial resistance screening in some specific environments, to identify contamination hotspots and emissions;

2.3.6. Enhance the sustainability of all streams of waste in the health sector by conducting a life cycle impact assessment in regulatory approval and incentivizing the reduction of impact of products and disposal practices.

Source: Convention on Biological Diversity. Biodiversity and health (CBD/SBSTTA/24/9). Adopted: 2021.

Environmental impact assessment

The environmental impact assessment or EIA is a tool of environmental management, "a national procedure for evaluating the likely impact of a proposed activity on the environment". This definition is sourced from the *Convention on Environmental Impact Assessments in the Transboundary Context* (1991) by the United Nations Economic Commission for Europe (UNECE). Although the focus of this instrument is on *transboundary* impacts, the objectives of this text are to prevent, reduce and control significant adverse impacts on the environment from certain activities. In accordance with this Convention, EIAs should be conducted for certain activities at an early stage of planning.

Under the Convention's *Protocol on Strategic Environmental Assessment (2003)* the linkage with health is explicit in the objectives, i.e. that "environmental (including health)" considerations are made with respect to development programmes, legislation and other mechanisms for sustainable development. The CBD calls for the use of appropriate procedures for EIA in certain cases. Under Article 14, EIAs should be required where projects "are likely to have significant adverse effects on biological diversity with a view to avoiding or minimizing such effects and, where appropriate, allow for public participation in such procedures."

The EIA mechanism appears in many other MEAs and other international agreements. Article 206 of the UNCLOS requires states to assess the potential effects of planned activities under their jurisdiction on the marine environment. Recommendations addressing impact assessments are also featured in the *United Nations Framework on Climate Change Convention (UNFCCC)*, as well as in the *Kyoto Protocol*. Principle 17 of the *Rio Declaration on Environment and Development (1992)*, a non-legally binding yet authoritative 'soft-law' instrument, states that EIAs should be carried out for activities "that are likely to have a significant adverse impact on the environment and are subject to a decision of a competent national authority". The types of activities that may create such impacts could include livestock, crop and aquaculture farms, veterinary clinics, or VMP manufacturing (or waste management) facilities.

For more on how EIA can be used as tools to mitigate the impacts of AMR, see Section 8.2.8 of this Study.

Transparency and Pollutant Release and Transfer Registers

Transparency is a fundamental principle of good governance. Legislation that reflects the norms enshrined in the *Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters (Aarhus Convention)* by the UNECE, enables a greater body of information to be available to the public on the environmental dimensions of AMR. These norms for transparency include the right of the public to: (i) access environmental information; (ii) participate in environmental decision-making; and (iii) to challenge public decisions that are not based on the preceding two principles. The *Kyiv Protocol on Pollutant Release and Transfer Registers* to the Aarhus Convention requires countries to set up publicly available pollutant release and transfer registers. The data is gathered from industrial sites and other sources, including intensive rearing of poultry and pigs and intensive aquaculture, waste and water management, and pharmaceutical production.

Water

Water bodies may spread resistant microorganisms between and among people, animals and other environmental reservoirs (UNEP, 2022). The right to a clean and safe environment has been recognised as a human right by the Human Rights Council in 2021 (A/HRC/RES/48/13) and the General Assembly in 2022 (A/RES/76/300). Similarly, the right to clean drinking water and sanitation was also recognised as a human right by resolutions issued by these bodies (A/HRC/12/50 and A/RES/64/292 respectively).

A multi-sectoral approach to integrated water resources management is advocated by FAO under the One Water One Health concept of water, reflected in SDG 6. This approach recognizes that decisions regarding land and water use have specific implications for public health. Less resilient ecosystems, shifts in patterns of disease, and AMR emergence and spread, may result where insufficient attention is paid to this interconnection. FAO's One Water One Health concept provides an integrated water resources management approach that embraces the value of water in all its forms and recognizes the intrinsic role of water in the protection of human, animal and ecosystem health (FAO, 2020b).

While the One Water One Health paradigm may be recent, older instruments such as the UNECE *Convention on the Protection and Use of Transboundary Watercourses and International Lakes (1992)*, which was opened to global accession in 2016, advocates an integrated water management approach. This is a mechanism for coordinated management of land, water, and related resources in support of sustainable water use. Therefore, this approach necessarily involves a consideration of land use planning (e.g. sites for pharmaceutical manufacturing, permissible sites for effluent discharge, or agricultural production sites). Though its scope includes only transboundary water bodies, this legally binding instrument seeks to strengthen *national* measures to manage transboundary surface waters and aquifers. Article 3 stipulates that parties are to prevent, control and reduce water pollution from point sources by requiring authorizations for wastewater discharges, and that such authorized discharges are to be monitored and controlled by the competent national authority. Interstate cooperation mechanisms are established to identify pollution sources and collect related data. Article 11 requires parties to establish pollution parameters and the specific pollutants that will be subject to periodic monitoring. The Convention's *Protocol on Water and Health* addresses the linkage between promoting human health and reducing water-related diseases by protecting water sources through effective mechanisms for management and sanitation. A 'water-related disease' is defined to mean any adverse effects on human health that results from the quantity or quality of any waters. Article 4 specifically calls for effective protection of water resources from pollution derived from agriculture, industry and other discharges and emissions of hazardous substances. Such protection should seek to reduce and eliminate hazardous discharges. It also recognizes that safeguards are needed against risks to human health from the use of wastewater for irrigation used in agriculture or aquaculture.

The *Convention on the Law of the Non-navigational Uses of International Watercourses of 1997 (UN Watercourses Convention)*, pertaining to the uses and conservation of all waters that cross international boundaries, including both surface and groundwater, requires states to take reasonable steps to control damage, such as caused by pollution or the introduction of species not native to the watercourse. This Convention also imposes an obligation on states that damage a shared water resource to take steps to remedy the damage or to compensate the sharing states for the loss.

Wetlands

Antimicrobials find their way into the natural environment via wastewater discharge and via run-off from farms and other sources into water bodies. For this reason, water sources are particularly sensitive to the build-up of antimicrobials. Wetlands with their range of dependent flora and fauna are also particularly susceptible. The *Convention on Wetlands of International Importance especially as Waterfowl Habitat of 1971 (Ramsar Convention)*, governs the conservation and 'wise use' of wetlands and their resources. The Convention establishes a framework for designating certain wetlands as Ramsar sites, which confers a specific status for protection based on their importance in terms of ecology, hydrology, zoology, or other significance. Ramsar Technical Report No. 7 on *Guidelines for Assessment, Monitoring and Management of Animal Disease in Wetlands* recognizes that antimicrobial-resistant pathogens drive disease emergence in wetland systems (Cromie *et al*., 2012).

The UN Watercourses Convention previously mentioned, sets up details for the protection and preservation of ecosystems, including wetlands in transboundary basins around the world.

Climate change

Climate change can have an impact on AMR. In recent years, it has become evident that temperature plays a key role in cellular, physiological, ecological, and evolutionary processes that affect the survival of bacteria (Rodriguez-Verdugo *et al*., 2020). In addition, as highlighted by the Intergovernmental Panel on Climate Change, a changing climate leads to changes in the frequency, intensity, spatial extent, duration, and timing of weather and climate extremes, and can result in unprecedented extremes (Seneviratne *et al*., 2012). Extreme weather events have an impact in the transmission of AMR; extreme temperatures and antimicrobials harm cells through many different pathways and mechanisms of action. Some of the cellular processes damaged by antimicrobials overlap with those affected by changes in temperature (Rodrigues-Verdugo *et al*., 2020).

Climate change can expand the distribution of infectious diseases and facilitate the emergence of others (WHO, 2017d), leading to a greater need for – and increased potential misuse of– antimicrobials. Climate change mitigation and adaptation strategies contribute to more abundant and safer freshwater and food, as well as healthier populations generally (WHO, 2017d), both animal and human, contributing to lower needs for antimicrobials.

While a variety of MEAs have been adopted to combat climate change, including the UNFCCC which entered into force in 1994, the landmark *Paris Agreement* is highlighted in this Study. The Paris Agreement is a legally binding international treaty that aims to keep the global temperature rise during the twenty-first century well below 2 °C above pre-industrial levels and to pursue efforts to limit the temperature increase even further to 1.5 °C. Additionally, the Paris Agreement aims to strengthen the ability of countries to deal with the impacts of climate change. One of the main obligations established under the Paris Agreement is the preparation, communication and maintenance of nationally determined contributions (NDCs) (Article 4.2(1)). Most countries have included measures related to agriculture in their NDCs (FAO, 2020d). These measures may also influence the mitigation of AMR, as they include the adoption of techniques for improved residue monitoring and management, updates to manure handling, use of better-quality feed as well as improvements in breeding and animal health (FAO, 2020d). These and other activities recorded in the NDCs contribute to improved agricultural production practices and protection of natural resources.

3.8. International crime

Substandard and falsified medicines present a significant threat to the availability, access and distribution of quality VMPs, and thus are also a risk for the spread of AMR. Enforcement provisions in national legislation including risk-based control systems may be guided by the *Convention on the counterfeiting of medical products and similar crimes involving threats to public health (2011)*, also known as the Medicrime Convention. This instrument seeks to improve the response to criminal acts related to the production and trade of falsified medicines (including VMPs), by asking State Parties to introduce provisions into their legislative frameworks which recognize these acts as offences and establish appropriate criminal sanctions. The Convention applies to all medicinal products, including VMPs (Article 4), without reference to whether they are protected under intellectual property rights or not, or whether they are generic or not (Article 3). Specifically, the following should incur criminal penalties: the manufacturing of falsified medicines (Article 5); the supply, offer for supply or distribution of falsified medicines (Article 6); and the falsification of related documents (Article 7). One of the striking features of this Convention is that it responds to the way in which organized crime infiltrates legal supply chains or authorized economic operators. Thus, corporate liability is established for legal persons involved in the aforementioned illicit activities (Article 11). Finally, the Convention calls for State Parties to use investigative techniques in cases related to falsified medicines including financial investigations or covert operations (Article 16). Specific articles are dedicated to enhancing cooperation between national agencies (Article 17) as well as international police and judicial cooperation (Article 21).

4. Frameworks addressing antimicrobial resistance at the regional and national level

Different regions worldwide may have instruments that address AMR with varying legal implications (and legal status) for national legislation. This section highlights AMR-related initiatives in various regions, which may influence National Action Plans (NAPs) as well as national legislation.

4.1. Regional directives, guidelines or strategies

Association of Southeast Asian Nations

The Association of Southeast Asian Nations (ASEAN) region has produced three main instruments indicating their commitment to address AMR. The first is the *ASEAN Plus Three Leaders' Statement on Cooperation Against Antimicrobial Resistance (2018)*. In addition to ASEAN Member States, the Republic of Korea, China and Japan are included in the Statement. This instrument supports the formulation and implementation of NAPs on AMR through the One Health approach. The Statement encourages the One Health approach more broadly, including through public health capacity-building activities, innovative public-private partnerships and incentives, and policy dialogue with relevant stakeholders. The Statement promotes the sharing of information on best practices and regulatory systems, as well as on technology to address AMR.

The *ASEAN Leaders' Declaration on Antimicrobial Resistance (2017)* prioritizes combatting AMR through a One Health approach, and outlines commitments towards an ASEAN strategic plan which advocates among other areas: a strengthening of regulatory systems; pharmaceutical and food supply chain management; health financing mechanisms; agricultural value chain management and environmental management; and enhancing regulatory mechanisms for VMP availability and distribution (primarily through the use of prescriptions); and phasing out the use of antimicrobials as growth promoters in the absence of risk analysis.

The *ASEAN Regional Strategy on Antimicrobial Resistance Communication and Advocacy (2016)*, sets out guiding principles on and a strategic framework for, communication for stakeholder engagement. Specific objectives are focused on prudent use of antimicrobials and good animal husbandry practices.

European Union

Early efforts on AMR began in the European Union region through the *Community Strategy against Antimicrobial Resistance (2001)*, which was later consolidated by the *Action plan against the rising threats from Antimicrobial Resistance (2011)*. In 2017, the latter was updated when the European Commission published *A European One Health Action Plan against Antimicrobial Resistance*, which supports the delivery of effective responses to AMR and promotes global efforts in mitigating AMR. It provides a framework for extensive action to reduce the emergence and spread of AMR, as well as to increase the development and availability of new and effective antimicrobials. The Action Plan is constructed on three pillars: (i) making the European Union a best practice region; (ii) boosting research, development and innovation; and (iii) shaping the global agenda. This Action Plan is recognized in *Regulation (EU) 2016/429 on transmissible animal diseases*, which emphasizes prevention of disease as a key means to reduce the use of antimicrobials.

The Regulation treats (and includes within its scope) microorganisms that have developed resistance to antimicrobials as if they were transmissible diseases, ensuring action can be taken against antimicrobial-resistant organisms when required.

In June 2023, the EU Council adopted a *Recommendation on stepping up the actions to combat antimicrobial resistance in a One Health approach* that encourages Member States to update and implement National Action Plans based on the One Health approach. Such Plans should, among other aspects strengthen coordination mechanisms for effective governance.

One of the objectives under the EU's *Farm to Fork Strategy (2020)* is to reduce overall EU sales of antimicrobials for farmed animals and in aquaculture reduce sales by 50 percent by 2030. The *EU Regulation 2019/6 on Veterinary Medicinal Products* and the *EU Regulation 2019/4 on Medicated Feed* support implementation of this goal through their measures to promote prudent use of antimicrobials and the One Health approach. In addition, the *European Parliament Resolution 2019/2816(RSP) on a Strategic Approach to Pharmaceuticals in the Environment* addresses the environmental implications of VMPs (and human medicines) throughout the lifecycle. For a summary of regulatory actions taken by the European Union, please see Appendix 1 of this Study.

Mercado Común del Sur

The MERCOSUR alliance, or the Southern Common Market trading bloc of South America, established a *Regional Action Plan to Combat Antimicrobial Resistance* in 2018. This Plan embraced three pillars: (i) the promotion of regional best practices, based on sound evidence, coordination and monitoring; (ii) the reduction of knowledge-based gaps and exploration of solutions to better address prevention and treatment of diseases; and (iii) the strengthening of the trading bloc's efforts to align with increasingly interconnected international actions and goals. To increase knowledge development for AMR, the Plan calls for the strengthening of surveillance mechanisms, including the revision of legislation for surveillance, to take into account scientific developments on data collection. Legislative reforms should also target communication regarding diseases transmissible to humans and harmonized rules for monitoring. The Plan specifies that Member States should keep abreast of all the latest developments relating to legal mechanisms, and accordingly, evaluations of the adequacy of implementation should be undertaken – for example relating to animal production laws and VMP laws.

Some key actions identified in the Plan include: strengthening the knowledge base regarding factors that give rise to resistance; strengthening the understanding of AMR, including its spread and build-up in the environment; improving implementation of the regulatory framework; monitoring AMR and strengthening detection systems; promoting the prudent use of antimicrobials; establishing harmonized surveillance systems; supporting studies investigating the prevention and treatment of diseases; and developing new diagnostic tools, treatments and alternative remedies, such as preventive vaccines.

South African Development Community

The *Harmonisation of Registration of Veterinary Medicinal Products (2017)* produced by the South African Development Community (SADC) recognizes the need for good quality and safe VMPs for livestock producers. Recalling VMP registration challenges in some countries, the SADC instrument seeks to promote a harmonized registration system, with appropriate requirements for different categories of VMPs. An added benefit is that industry will no longer face a multiplicity of procedures currently in place in different SADC Member States. The SADC text identifies roles for each of the following actors in the harmonized registration system: the competent authorities for drug registration (where different than the competent authorities for veterinary services), industry actors, the SADC Secretariat, the WOAH, and the African Union technical agencies (AU-PANVAC and AU-IBAR) and GALVmed.

4.2. National Action Plans and Strategies

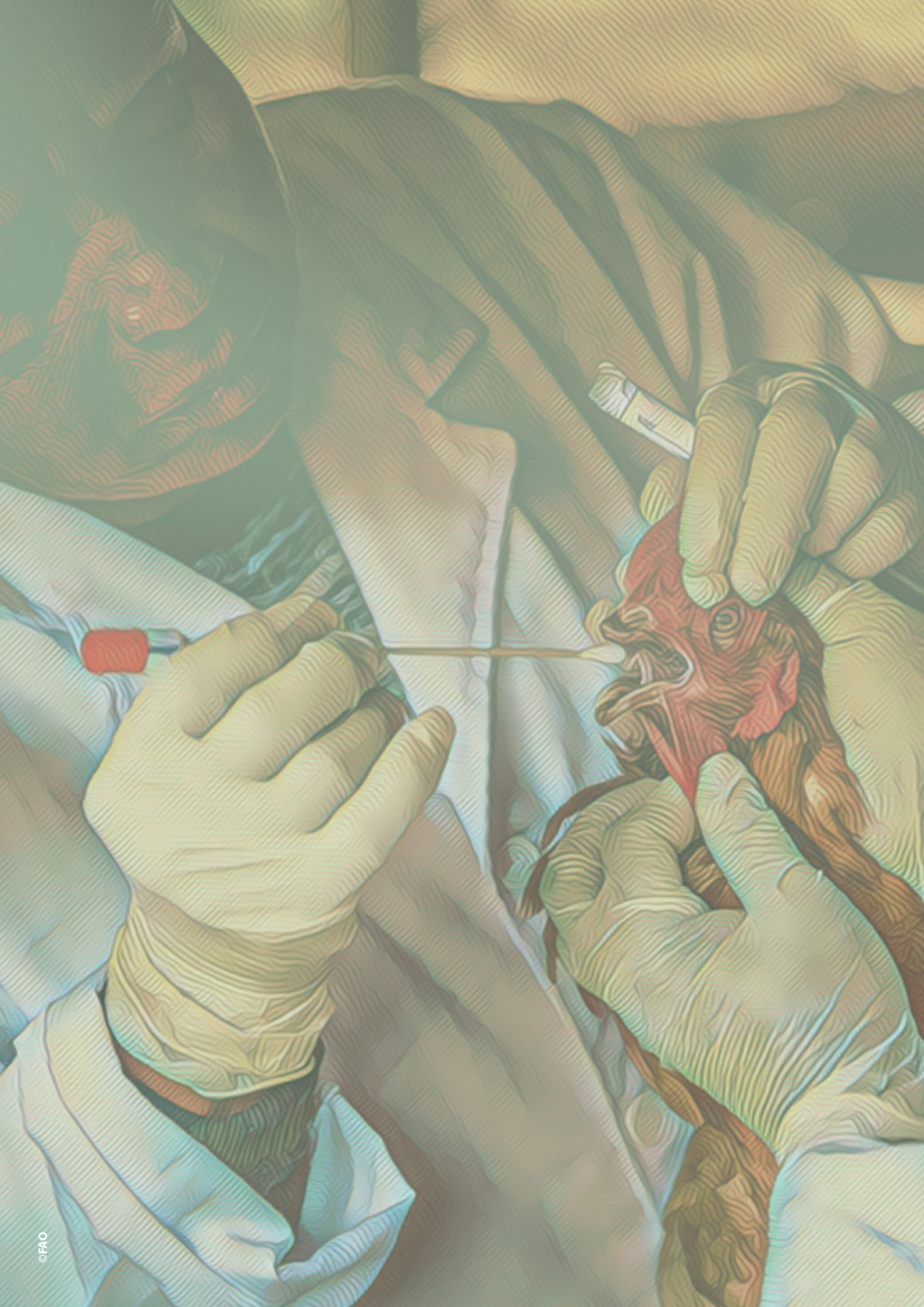
The *Global Action Plan on Antimicrobial Resistance* recommends that countries develop and implement an NAP to implement the Global Action Plan's objectives. The NAPs should assess resource needs and priorities, espouse appropriate governance arrangements for a multisectoral approach and set out a template for action. Specifically, NAPs should be predicated upon Global Action Plan principles including: (i) adopting a One Health approach; (ii) prioritizing a preventive approach; (iii) emphasizing sustainability of interventions; and (iv) developing incremental targets for implementation. A review of the content of, or challenges relating to, NAPs is beyond the scope of this Study. Instead, the following paragraphs introduce a cross-section of the various elements and priorities with *legal implications* identified in selected NAPs. Section 6 of this Study examines in greater detail the institutional arrangements for coordination of AMR responses at country level.

Calls for regulatory interventions feature in varying degrees in NAPs, and in some cases almost not at all. This may depend on the adequacy of the existing legal framework as perceived by authorities and stakeholders at the time of development of the NAP, or on the identification of higher priority actions. For example, both India's and Afghanistan's NAPs on AMR (both issued in 2017) identify the need to strengthen the legal framework for antimicrobial control, including: (i) the regulation of prescriptions and dispensing of antimicrobials; and (ii) the organization of consultations among regulatory bodies in order to review legislation on antimicrobials, and to identify additional regulatory interventions that may be required.

Other NAPs go a step further in the degree of specificity of legislative reforms that will be required to address AMR. This may demonstrate that those countries conducted some form of (legislative) assessment to determine the specific gaps identified in the NAP. For example, Oman's NAP on AMR (2017) points to legislative provisions to address specific lacunae, such as: requirements for manufacturers and importers to collect and report data on VMP distribution; frameworks for VMP efficacy, quality and safety; strengthening and clarifying rules related to prescription and dispensing of VMPs; prohibiting the use of critically important antibiotics in animals; and phasing out the use of antimicrobials for growth promotion.

In other countries, the focus is much narrower still. In Brazil's NAP (2018), legislative updates are targeted at the advertising of VMPs (under a broader scheme to encourage rational use in livestock production). Kenya's NAP (2017) identified the legal framework for animal identification and traceability as requiring an update. To illustrate other non-legislative aspects canvassed as priorities, emphasis in the Kenya NAP was placed on the development of partnerships, on effective education and training, and finally, on sustainable investment options for medicines, diagnostic tools and vaccines.

Even where the existing legal framework for the various elements relevant to AMR is already advanced, some countries recognized the need to keep abreast of political and scientific changes. The United Kingdom of Great Britain and Northern Ireland's NAP (2019) recognized that lists of priority contaminants of concern (including antimicrobials) and their corresponding standards would be reviewed in line with future developments. In addition, to improve antimicrobial quality, actions were identified to mitigate risks of illegal sales, for example, through robust enforcement and participation in regional and global cooperative actions for this purpose.



5. Preliminary considerations for analysing antimicrobial resistance relevant legislation

5.1. Framework for analysis used in this Study

Across the regulatory areas examined in the sections that follow, there is a range of principles, tools and mechanisms highlighted that are relevant to AMR. Regulators may use the sections that follow to: (i) compare their existing legal framework as benchmarked against these elements (and the international standards and requirements from which they derive) and thus identify key gaps and weaknesses in their frameworks; and (ii) identify ways to introduce additional regulatory control elements or better mitigate AMR consequences through legislation, should this be considered feasible in the national context. The identification of *which* particular element (or combination of elements) would be the most impactful and effective in a particular national context is very context specific. Such a determination is dependent on, among other factors, the specific country needs, its resources, its regulatory strengths, the broader legal and governance framework, and the agriculture context. Furthermore, it should be recalled that regulatory reform involves an extensive examination of a range of legislation as well as stakeholder engagement before recommendations can be made.

5.2. Types of laws and legislative provisions to address antimicrobial resistance

Section 1 of this Study underscored that, in general terms, legislative provisions to address AMR do not need to be AMR-*specific*. Laws may be effective in the absence of specific references to AMR-related considerations or parameters, provided there is an enabling provision that can broadly cover the obligation, rule, standard, behaviour or penalty. 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 their existing water management schemes and practices. General enabling legislation may be easily modified – particularly at the secondary legislation level – to include AMR considerations.

In the Sections that follow, for each regulatory area or topic highlighted below, the discussion explores the diverse (sector) sources of legislation that may contain relevant provisions. Such provisions may be found across a range of several types of laws. For example, regulatory elements pertaining to VMPs may be regulated in instruments governing animal production, aquaculture, combined with human medicines, or in self-standing VMP legislation. In the same vein, it is possible that a single legal instrument governs more than one of the areas identified. Therefore, it is important to understand that legal frameworks addressing AMR will necessarily vary from jurisdiction to jurisdiction. Put differently, AMR considerations may be incorporated into laws of varying scopes.

On one side of the spectrum, legislators may specifically create laws with a broad scope, covering various aspects related to public health, food and agriculture or encapsulating a One Health approach. Broad legislation may also contribute to harmonizing AMR response efforts in the food and agriculture sector.

However, broadly scoped laws would not generally address the specific regulatory elements that may be required in specific sectors. Instead, this approach may be useful to address intersectoral elements that may require the intervention of multiple entities to be implemented and to foster coordination. This is the case, for instance, of legal instruments specifically drafted to set up governance arrangements for AMR or institutional coordination (see Section 6 of this Study).

The United States of America and the Philippines provide examples of countries that have promulgated legislative instruments with a broad scope. In the United States, the *Executive Order – Combatting Antibiotic-Resistant Bacteria (2014)*, among other legislation, sets the overall policy direction of the country's fight against AMR and brings together high-level oversight and coordination institutions, and tasks them with the development and implementation of Federal Government policies to combat antibiotic-resistant bacteria. Furthermore, it establishes guidance on improved antibiotic stewardship, national AMR surveillance and the prevention and response to infections and outbreaks with antibiotic-resistant organisms. The *Presidential Administrative Order No. 42* of the Philippines provides another example of a legislative tool establishing multi-sectoral collaboration for AMR, by establishing the Inter-Agency Committee for the formulation and implementation of a National Plan to Combat Antimicrobial Resistance in the Philippines. The Order defines both the composition and functions of the Committee and provides for the key content to be included in the National Plan.

Beyond institutional coordination, the *Regulation on the monitoring of zoonoses and zoonotic agents, antimicrobial resistance and food-borne outbreaks (2011)* of Türkiye, aims to ensure that these zoonotic issues are properly monitored to enable the collection of necessary information to evaluate relevant trends and sources. The Regulation tasks the ministry responsible for food, agriculture and livestock – together with the ministry responsible for health, where necessary – to ensure that comparable data on the development of AMR is monitored and collected. The monitoring shall be done in accordance with the legislation of the ministry responsible for health on the monitoring of human isolates, with some specific requirements related to animal species, bacterial species and antimicrobials themselves, included in the monitoring schemes (Article 9).

On the other side of an over-arching legislative response spectrum, regulators may choose to adopt legislation with a narrower scope, addressing only individual elements that would usually be found in a specific sector. Such narrow-scope approaches may be used, for instance, to target a type of agricultural practice (e.g. prohibit such practice). A fitting example is the restriction or prohibition of the use of antimicrobials as growth promoters (for more on this topic see Section 7.1.12 of this Study). As an example of legislation, Egypt has adopted *Resolution No. 2721 of 2004* which provides for the absolute prohibition of antibiotics as a growth stimulator in forage and fodder used for poultry and fish.

The benefit of narrow legislative intervention is that it allows the regulator to draft precise responses to specific problems. The risk of such an approach is the fragmentation of the legislative framework in the corresponding sector, with possible gaps, overlaps and inconsistencies, unless care is taken to ensure consistency across various legal instruments. Narrowly scoped legal instruments may also fail to consider the complexity and interconnectedness of the whole phenomena of AMR, potentially leading to less effective solutions in the long term.

6. Intersectoral regulatory responses to antimicrobial resistance

6.1. Coordination

Introduction

The One Health approach embraces the notion that the health of humans, animals and ecosystems are interconnected (see Section 1.2). Such an approach requires a coherent regulatory and institutional framework with linkages that enable coordination and appropriate integration of the range of tools across the sectors canvassed in foregoing sections. A collaborative approach is needed to bridge different perspectives and various levels of resources, as well as to enable a multipronged response to the many discrete drivers of AMR. To tackle AMR, the WHO points out that time, money, technical expertise and human resources are required to cement coordination across sectors and to secure trust and ownership (WHO, 2018). The importance of coordination was highlighted in the Global Action Plan which recommends the need for cooperation among "human and veterinary medicine, agriculture, finance, environment, and well- informed consumers" (WHO, 2015). The Global Action Plan further urges the establishment of national and local governance arrangements (Paragraph 49). This was elaborated by the IACG in its call for "effective national coordination, accountability and governance mechanisms that ensures collaboration between government ministries, parliamentarians, civil society organisations, the private sector and regional and international partners." (IACG, 2019, p. 12).

Stakeholders

Stakeholder engagement is the means to facilitate both a bottom-up and top-down approach. An AMR multisectoral coordination body should include representation of the competent authorities for human health, animal health, plant health, food safety, the environment and agriculture both at national and local levels. Coordination may be led by any supra-ministerial body, such as the Council of Ministers or Prime Minister's Office. In addition to the line ministries, other stakeholders include funding organizations, laboratories, veterinary statutory bodies, farmers and related organizations and associations, pharmaceutical and pesticides industries and other private sector representatives, non-governmental organizations (NGOs), consumer associations, academia, and regional and international partners. Whether or not private stakeholders are directly included in decision-making or members of the coordination body or as part of an advisory body, the participation of this group is important. Where private sector representatives are included in the coordination body and such body is granted with executive or regulatory functions, it is important to ensure that there are mechanisms in place to prevent potential conflicts of interest.

Legislation to establish institutional arrangements

A coordination body should have a clear mandate, ideally established by legislation. Without a legal foundation, the coordination entity is exposed to fluctuating political will, and accountability and transparency are reduced; ultimately, the lack of legal basis results in reduced effectiveness and sustainability (Chua *et al*., 2021). Several countries have used legislation to establish such coordination arrangements for example: Senegal in its *Arrêté portant creation et fixant les règles d'organisation et de fonctionnement de la Structure de Coordination multisectorielle de la Securite Sanitaire Mondiale (SSM) One Health (No. 21787 of 2017)*; Ecuador under the *Acuerdo Interinstitucional – Crea el Comité Nacional de Prevención y Control de la*

Resistencia Antimicrobiana (Nº 1-2020); and Mali through its *Décret portant création, attributions, organisation et fonctionnement de la Plateforme «Une seule santé» au Mali (No, 2018-0369/PR-RM of 2018)*.

Legislation should establish the mandate and composition of the coordination body (the latter will be dependent on the former). The entity may be an advisory body or an information exchange mechanism. Alternatively, it may be an executive body requiring action, compliance or enforcement by line ministries. The needs of countries may differ on the scope of functions of the coordination body, with different points of emphasis. There are a range of configurations possible, relating to the functions and composition of such a body. Common mandates include coordination and cooperation in: (i) the development, oversight and implementation of AMR policies, the NAP and related programmes, including updating goals and priorities; (ii) development of the knowledge base for policies and guidelines; (iii) establishment of an integrated surveillance system for AMR; (iv) development and implementation of programmes (e.g. education-based Antimicrobial Stewardship Programmes, research and development initiatives and joint monitoring systems); (v) mobilization of resources, budget management and investment; (vi) facilitation of public-private partnerships; (vii) proposing regulatory measures for the ministers' approval; (viii) fostering coordination among inspection and enforcement bodies; and (ix) facilitating the collection of data and ensuring information exchange among ministries. The entity may establish the strategy and goals and may also support or direct how resources are allocated. Additionally, the entity may establish programmes for operational-level activities and coordinate technical, lower-level actions. Implementation of AMR activities and addressing AMR at country level may take place primarily in working groups that have clear timelines and deliverables (WHO, 2018). The US *Executive Order – Combating Antibiotic-Resistant Bacteria (2014)* states that combating antibiotic-resistant bacteria is a national security priority (Section 2) and creates a multisectoral Task Force to respond to it (Section 3). The Task Force is required to submit 5-year National Action Plans to implement the National Strategy for Combating Antibiotic-Resistant Bacteria (Section 3). The Task Force must also define, promulgate and implement stewardship programmes in healthcare settings, and coordinate with the authorities responsible for food safety, drug administration, and agriculture, to assist in taking steps to eliminate the use of medically important classes of antibiotics for growth-promotion purposes in food producing animals. National surveillance efforts are to be undertaken with the environmental authority (Section 6).

Legislation may designate a lead ministry (including through a mechanism for rotating the lead or chair of the body) and may also provide a procedure to incorporate new members into the body or its working groups where these exist. A coordinating body for AMR should have an established budget (an identified budget source). Many bodies that have sound legislation to support their functions fail operationally for lack of funding of its activities. Legislation should establish an accountability framework, including indicating to whom the body is accountable (such as a specific ministry, the council of ministers, or other). The legislation should also enumerate any mechanisms for reporting and information exchange among constituents, as well as for monitoring. A Secretariat may be established to assist the functioning of the coordination entity, and may determine the rules of procedure, such as the conduct of meetings, quorum, etc. (which may also be outlined in legislation) so that there is transparency in functioning and decision-making. Senegal's *Arrêté No. 21787 of 2017,* mentioned previously, establishes a Permanent Secretariat for the relevant coordination entity (Article 6). This Permanent Secretariat comprises a representative of the Prime Minister and is assisted by a multidisciplinary team. Their key responsibilities include the preparation of meetings and assisting the coordination entity in their mission.

Any coordination mechanism would need to be tailored to the specific fundamental administrative divisions in the country, considering horizontal pillars (across ministries) as well as vertical pillars (between the central and the decentralized levels), as well as coordination within governmental institutions. Coordination is also required at strategy (policymaking) level and at operational level for effective coherence. Legislation should underpin the network of roles and responsibilities across sectoral (horizontal) collaboration as

well as vertical coordination from central to local/municipality/village level. The national constitution or similar fundamental laws of a country normally define the responsibilities between the central level and various decentralized levels (starting with the state, region, province or canton level). 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 similar fundamental 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, trade, and in matters related to health hazards that may have an impact across the entire territory or that may have transboundary impacts. Thus, countries should consider how responsibilities over areas such as agriculture (disease control and production), environmental matters, and public health, are shared at decentralized or central level.

6.2. Intersectoral legislative responses to antimicrobial resistance

Some countries may choose to enact *self-standing legislation* specific to AMR or include *AMR-specific provisions* in broader legislation. This strategy is designed to target cross-cutting or multidisciplinary areas and bring together the range of actors involved in AMR responses in a single piece of legislation. Such laws may be based on any regulatory needs identified in the AMR policy or NAP. It is possible that the development and coordination of such intersectoral legislative responses are under the aegis of the AMR coordination mechanism outlined in the foregoing section.

As a preliminary point, such legislative interventions should ensure policy coherence *across* AMR-relevant sectors and should be *inclusive* of all sectors relevant to AMR. A second (related) priority is that the cross-cutting or multidisciplinary law or legal provisions should not result in the duplication of functions under sectoral governance, nor should any gaps or weaknesses in sectoral governance be filled with an overarching instrument that would create fragmentation or inconsistencies in the legal framework. With the *exception* of legal instruments addressing the institutional framework or setting out intersectoral responses, AMR-specific legislation must avoid creating substantive provisions that regulate a sector that should be addressed in sectoral legislation. Finally, AMR-specific provisions should not modify the division of functions and mandates established in sectoral legislation, except for what is necessary to facilitate coordination.

Any new legislation should adequately respond to the specifics of national and local needs, priorities and challenges, while being guided by international strategies. The law or provisions should further develop the principles of accountability, transparency, stakeholder participation and other recognized principles of good governance. Intersectoral legislative responses to AMR may be focused on, aspects such as: integrated surveillance, the joint implementation of a specific AMR programme, financing, and awareness-raising. Ideally, the legislation should set out the lead entity, the respective responsibilities of participating ministries and the role of the private sector where involved. In addition, the specific processes and mechanisms for coordination, information exchange and multi-sectoral responses should be included.

The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) is a national integrated surveillance programme that spans across humans, animals, and retail meat and is established to collect, analyse, and communicate trends in antimicrobial use and AMR. There is no dedicated single legal instrument specifically for the establishment of CIPARS, instead the underpinning legal framework comprises the existing data collection and record-keeping provisions across different laws which serve as sources of data for the programme. These laws include the *Food and Drugs Act (R.S.C., 1985, c. F-27)*; the *Food and Drug Regulations (C.R.C., c870)*; the *Aquaculture Activities Regulations (SOR/2015-177)* and the *Pest Control Products Sales Information Reporting Regulations (SOR/2006-261)* (CIPARS, 2002, p. x).

6.3. Private sector participation in antimicrobial resistance

Governance for AMR that is inherently multisectoral and cross-cutting is potentially very complex, specifically where governance is understood as a diffuse and collaborative system contributed to by a broad array of public, private and non-governmental actors, rather than a state-centric government-led process (Kickbusch and Gleicher, 2012). It is therefore important to optimize the role of each interest group in contributing to processes and outcomes that lead to effective AMR governance. Stakeholder engagement is a central tenet of legislative reform and in securing compliance with rules. Legislative frameworks that support information sharing and collaboration help cement a unified vision towards goals.

While this Study focuses largely on the (public/governmental) regulatory aspects of AMR, it is important to highlight two major regulated groups: the general public (i.e. citizens and natural persons within a jurisdiction) as well as the various industries that impact and are impacted by the regulatory framework for AMR. Industry operators for VMPs (as well as feed and pesticides) have a role in adhering to rules on the authorization and distribution of antimicrobials, as well as in limiting the environmental negative externalities of their operations. Livestock and aquaculture farmers contribute to the responsible and prudent use of antimicrobials, including by taking steps to prevent disease and adhering to good agriculture practices. Veterinary professionals also have a role in supporting the responsible and prudent use of antimicrobials through obligations relating to the issuance of prescriptions and record-keeping. Private laboratories may have a role to play as official laboratories, where so designated by the competent authority, and in contributing to surveillance networks.

Sound regulatory frameworks will explore ways to eliminate economic incentives that encourage inappropriate use of antimicrobials and may introduce incentives that optimize use (WHO, 2015). The Global Action Plan also highlights the role of public-private partnerships as a vehicle "to ensure equitable access to quality-assured products … through fair pricing and donations for the poorest populations" (WHO, 2015, p. 4). Supporting legislation may be developed for public-private partnerships that offer a range of important AMR solutions, including stimulating the research and development of new antimicrobials, establishing surveillance networks and developing laboratory infrastructure.

There are different examples of private sector led initiatives to reduce or control the use of antimicrobials, including self- and co-regulation initiatives, NAPs led by the private sector, and participation in advisory or executive committees led by the public authorities. In Belgium for example, 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. This was affected through the signing of a Covenant between the Federal Government and all relevant sector partners for reduced use of antimicrobials in the veterinary sector (AMCRA, 2018).

The private sector in many countries has adopted a range of voluntary initiatives as part of their sustainable business agendas. Whether under the leadership of global coalitions such as the AMR Industry Alliance that sets out sustainable solutions for industry actions impacting AMR, or at the level of individual businesses, the private sector can undertake AMR-specific sustainability assessments, modify their operational practices accordingly and report on the impact of their changes.

7. Legislation regulating antimicrobials

7.1. Veterinary medicinal products

One of the most important regulatory areas for curbing the development and spread of AMR in food and agriculture is the regulation of VMPs containing antimicrobials. These may include antimicrobials for terrestrial and aquatic animals, as well as other medicinal products such as vaccines or biologicals. Antimicrobials are used for disease treatment and prevention, and in some countries, for non-veterinary medical uses, such as to stimulate animal growth. Particularly in the latter case, low dosages (that are not effective to kill pathogens) can, over an extended period of time, heighten the risks of AMR by creating a selective pressure for resistance. Because antimicrobials might be used in animal production to offset poor hygienic and biosecurity conditions (as well as other factors such as poor nutrition and welfare), the promotion of animal health frameworks as a means to reduce antimicrobial use in production are also important and explored further in Section 9 of this Study. Since antimicrobials for animals are most often regulated within broader legislation on VMPs, this Study will use the term "VMP" to refer to them.

The regulation of VMPs should cover the entire lifecycle of the product including authorization/registration, production/manufacturing/compounding, import, export, prescription, distribution, transport, storage, advertisement, labelling, packaging, sale, use and disposal. Also included in this lifecycle approach is the treatment of obsolete and unused VMPs, residue monitoring, and treatment of packaging potentially contaminated with antimicrobials. A lifecycle approach will identify the respective responsibilities of competent authorities in regulating all the aforementioned stages, as well as the responsibilities of stakeholders throughout the chain. The latter includes VMP manufacturers and feed manufacturers that produce antimicrobials or active pharmaceutical ingredients, retailers, pharmacists, veterinarians, and farmers.

Distinguishable from the other regulatory areas identified in this section (such as food safety, water management or animal feed regulation), *all* the elements of the regulatory framework for VMPs have a potential impact on AMR. A deficiency in one aspect of VMP regulation alone may thus contribute to the rise of AMR.

Section 7 has been prepared using the following international standards as benchmarks: Article 3.4.11, Chapter 6.8 and Article 6.10.3 of the TAHC; Chapter 3.4 of the WOAH *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)*; and the Codex CXC 61-2005.

7.1.1. What is the purpose of veterinary medicinal products regulation?

Article 3.4.11 of the TAHC states that "*Veterinary legislation should provide a basis for assuring the quality of veterinary medicines and biologicals and minimizing the risk to human, animal and environmental health associated with their use.*" A VMP regulation should ensure that supplies of VMPs are safe, of good quality, and effective for their objectives. Sound regulatory control of VMPs contributes to "*responsible and prudent use*" as advocated by the WOAH in Chapter 6.10 of the TAHC. Gaps in VMP regulation have a knock-on effect that ultimately increase the risk of the spread of AMR in both animals and humans.

A VMP registration and control systems protect against distribution and consumption of products that are not authorized for sale in the country. This system also protects against products that are of poor quality, adulterated, falsified, substandard or expired. A VMP regulation also governs labelling requirements, which is important in order to convey pertinent information on aspects such as dosage, its use and precautions, considering that VMPs might be administered by non-veterinarians such as the livestock keeper.

Laws often explicitly state the purposes for regulation. The Japanese *Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (as amended in 2015)* takes an integrated approach to regulating, *inter alia*, pharmaceuticals for both human and animal use. Article 1 of the Act identifies as its objective, to improve health and hygiene through the control of the quality, efficacy and safety of pharmaceuticals. The Act also seeks to prevent health and hygiene-related hazards caused by the use of pharmaceuticals, including through research and development of pharmaceutical products which fulfil particularly high medical needs. Ethiopia's *Veterinary Drug and Feed Administration and Control Proclamation No. 728/2011* establishes in its Preamble that the purpose is to regulate the production, distribution and use of VMPs and to ensure their safety, efficacy and quality while enhancing the productivity and health of the livestock population. A second objective is established as preventing and controlling the illegal production and distribution of VMPs and their incorrect use.

7.1.2. Where are veterinary medicinal products regulated?

A VMP might be regulated in stand-alone VMP legislation or may be legislated together with medicines for humans (in pharmaceuticals legislation). Provisions for VMP regulation may also be found in in animal health and/or production legislation, or in 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. In some countries, VMPs are regulated with other agricultural inputs such as feed or agrochemicals. In addition, provisions for addressing falsified and substandard VMPs may be housed in consumer protection or product safety legislation.

7.1.3. Institutional coordination

Scope of laws and coordination

As noted in Section 7.1, the control of VMPs (including antimicrobials) should cover the entire lifecycle. This means that various competent authorities may be involved, although there should be a key entity that is responsible for VMPs specifically, or for all medicines (human and animal). The functions of an entity responsible for VMP management are identified below.

A critical requirement for the institutional framework is that the applicable legislation ensures coordination in the authorization and management of all types of VMPs (i.e. those for terrestrial animals and those for aquatic animals). In addition, VMP authorization/registration should be coordinated with that of human medicines authorization. Institutional coordination can take many forms, from overarching multi-agency decision-making bodies (joint authorization bodies) to more integrated day-to-day collaboration among different agencies (when such regular cooperation is feasible), to a third option where one agency participates in a decision-making process that is otherwise run by another. Norway aims for this latter coordination by having the same body – the Norwegian Medicines Agency – as the competent authority to authorize medicine for human use as well as for animal use, as established under the *Medicines Act (as amended in 2018)*.

Where the legal framework establishes a body specifically mandated to address VMPs, provisions for coordination may explicitly require collaboration, consultation or information exchange with the body responsible for controlling human medicines, or may require a representative of the latter to form part of a technical or advisory group under the body responsible for VMPs. Kenya's *Veterinary Surgeons and Veterinary Paraprofessionals (Veterinary Medicines Directorate) Regulations (No. 209 of 2015)* includes the Registrar of the Pharmacy Poisons Board among the representatives in the council that is responsible for approving authorization/registration of VMPs.

Another arrangement is evidenced in Sweden, where a coordinating mechanism was created in 2012 under the joint leadership of the Public Health Agency in collaboration with the Swedish Board of Agriculture. This mechanism enjoys the participation of 21 government agencies (Government Offices of Sweden, 2020). In Ireland, the Department of Agriculture, Food and the Marine (DAFM) is the competent authority responsible for legislation in all areas related to the manufacture, supply and use of veterinary medicines, including veterinary antibiotics (Department of Health, 2017). The VMPs must be authorized either by the Health Products Regulatory Authority (HPRA), which also authorizes human medicines ensuring efficient coordination of the two, or the European Medicines Agency. The DAFM, HPRA and the Pharmaceutical Society of Ireland operate a coordinated system of controls to monitor compliance covering the entire chain of veterinary medicines from manufacture to use (Department of Health, 2017).

National regulators are best placed to make the decision on appropriate structures as they have the best knowledge of how multi-agency cooperation works in their own country context. Having a joint authorization body, or an approval process with a high degree of integration of relevant disciplines and sectors, offers a more coherent VMP framework, avoids duplicative work, and makes better use of limited resources. These benefits can also be found in systems where the processes for authorization are separate; what is critical is a good degree of communication and collaboration. It is important that human and animal medicines are regulated in a coordinated manner, primarily to better address interdisciplinary matters such as restricting the use of medicines in animals that are critically important for use by humans (see Section 7.1.5). In addition, effective coordination reduces the likelihood of circumvention of more stringent systems by those wishing to register or use certain products. This has been experienced in some countries where, for example, an antimicrobial that is used in both human and veterinary medicine was governed by two different sets of standards and created regulatory loopholes.

Institutional arrangements are a core mechanism for effective coordination, although other provisions in the legislation should reflect this coordinated approach. Viet Nam's *Directive No. 37/2005CT-TTg* establishes that VMPs designated for livestock use should not be used in aquatic animals and vice versa. Under this instrument, the ministry responsible for trade is designated as having prime responsibility for ensuring the management of antimicrobials and other chemicals used in food and is required to cooperate with the ministries responsible for agriculture, fisheries, health, environment, and science and technology. Kenya's *Veterinary Surgeons and Veterinary Paraprofessionals (Veterinary Medicines Directorate) Regulations (No. 209 of 2015)* establishes the mandate of the Veterinary Medicines Directorate as the setting of standards for VMPs in such manner as to protect human health, animal health, and the environment, recognizing the interlinkages of VMPs in these three sectors.

Functions of the authority responsible for the control of VMPs

As there may be multiple competent authorities involved at country-level, regulators should identify which entities are responsible for: (i) authorization of VMPs; (ii) management of VMPs to ensure quality, safety and efficacy; and (iii) monitoring of antimicrobial use. Regulators should identify laws that empower an entity with the specific function or mandate listed below, as it is important to clarify the gaps and overlaps first and foremost in legislation before looking at any implementation gaps in practice. In some countries,

gaps in legislation are filled by authorities carrying out activities and functions for which they do not have the legal mandate, resulting in a lack of transparency and potential confusion. The identification of the competent authority 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 TAHC, as well as the CXC 61-2005, the competent authority should have the powers to:

(i) regulate the authorization of VMPs, including labelling, packaging, surveillance (both post-market pharmacovigilance as well as more general surveillance on the status of AMR in the country) and monitoring compliance;

(ii) grant marketing/manufacturing authorization to VMP producers, importers and 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 responsible and prudent use;

(v) develop up-to-date guidelines on data requirements for the evaluation of applications for the registration/authorization of antimicrobials;

(vi) approve national strategies to promote prudent use of antimicrobials, implement Good Production Practices, formulate vaccination policies and promote the development of animal health at the farm level;

(vii) actively combat the manufacture, advertisement, trade, distribution and use of illegal and substandard and falsified active pharmaceutical ingredients and products (through regulatory, monitoring and enforcement functions*);*

(viii) regulate the use of VMPs, with special focus on antimicrobials and critically important antimicrobials (WHO, 2017a) or antimicrobials of veterinary importance (OIE, 2021);

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

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

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

(xii) regulate the sale and advertisement 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; and

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

According to Article 6.10.3 of the TAHC, it is important that legislation safeguards against conflicts of interest of the relevant authorization body (or its composite members) that are of a commercial, financial, hierarchical, political or other nature, that may taint its decisions. Such provisions may include the duty to disclose a financial or other interest, or the prohibition of private sector representatives in authorization/registration or other executive bodies.

7.1.4. Definition of terms

How a term is defined by law affects the scope of application of the law. This is illustrated through the term 'animal' and whether this includes both terrestrial and aquatic animals, wildlife animals or pets. Similarly, the scope of manufacture or production may vary to include formulation.

A VMP legislation should provide definitions of key terms, such as "veterinary medicinal product" (some national laws may refer to "veterinary drug"), as well as "prevention", "control" and "treatment". Importantly, the definition of VMP should cover active substances or generic medicines that can be used directly or be used for VMP formulation. Also medicated feed may be expressly defined under VMPs so that feed containing antimicrobials may be regulated in the same manner as other antimicrobials (see Section 7.2 for more on antimicrobials in animal feed). While terms such as antimicrobial or AMR may not necessarily be featured in older legislation, this would be a useful inclusion when updating or revising legislation. Definitions of key terms are important for the smooth implementation of legislation and should be consistent with definitions in international standards like the Code of Practice CXC 61-2005 and the WOAH Animal Health Codes).

As an example, the European Union has adopted definitions for VMPs, AMR and antimicrobials. The *EU Regulation 2019/6 on Veterinary Medicinal Products* defines VMP in Article 4(1) as: "any substance or combination of substances which fulfils at least one of the following conditions: (a) it is presented as having properties for treating or preventing disease in animals; (b) its purpose is to be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; (c) its purpose is to be used in animals with a view to making a medical diagnosis; (d) its purpose is to be used for euthanasia of animals." The EU Regulation defines Antimicrobial resistance in Article 4(11) as: "the ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species." The EU Regulation defines Antimicrobials in Article 4(12) as: "any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals." A simpler definition comes from Canada (British Columbia), where the *Veterinary Drugs Act ([RSBC 2018] Chapter 363*) defines "veterinary drug" as: "(a) a drug used, or intended or represented to be used, as a drug for the treatment, prevention or diagnosis of a disease of an animal, and (b) a drug listed or included by reference in the regulations" (Section 1).

It is important to ensure that definitions adopted in veterinary legislation and those in laws governing human medicines are consistent so that the legal framework does not result in *de facto* gaps or overlaps of the types highlighted in the previous section.

7.1.5. Authorization or registration of a veterinary medicinal product

Overview of key regulatory elements for authorization/registration
• No VMP should be manufactured, imported, distributed, sold or used unless authorized/registered.
• Any exceptions to the requirement of authorization/registration should be clear and circumscribed, e.g. for research or for emergencies.
• Authorization/registration of veterinary (terrestrial and aquatic) VMPs should be coordinated with the authorization/registration of human medicines.

Overview of key regulatory elements for authorization/registration *(cont.)*

- Procedures for receiving and evaluating applications for authorization/registration should be established and clear.
- Decision-making criteria for authorization/registration should be clearly stated and should contribute to the goals of quality, safety and efficacy.
- All VMPs should be classified according to typology, potential hazards and requirements so as to indicate the restrictions which apply to their prescription and dispensing.
- Registration may stipulate specific conditions related to package and labelling requirements, advertising, storage, prescriptions and use, and disposal.
- A registry should be established of antimicrobials permitted for use on terrestrial and aquatic animals; this should be consistent with the WOAH *List of Antimicrobial Agents of Veterinary Importance*.
- Antimicrobials listed on the WHO *List of Critically Important Antimicrobials for Human Medicin*e should be restricted in veterinary use.

Rationale

The (market) authorization/registration phase determines *which* VMPs will be authorized for sale and *how* they can be used in the country. Authorization or registration of a VMP should consider the entire lifecycle of the product, from manufacturing to disposal of waste, including the potential contamination of soil, water and the environment with that waste at various stages in the lifecycle. The authorization/registration of antimicrobials used for human purposes and those for veterinary purposes should be coordinated as noted in Section 7.1.3. Authorization commonly takes the form of a registration scheme. The two terms (authorization and registration) are sometimes used interchangeably, or in some jurisdictions, one term may refer to a comparatively more simplified screening process than the other. This may on the account that the VMP has already been registered in another country or be based on a summary risk evaluation. A complete process refers to a full screening and testing of the product in the country based on a risk evaluation.

Procedures, decision-making criteria and transparency

Generally, applications for registration or market authorization should be submitted to the competent authority responsible for VMPs for evaluation. Legislation should enumerate the criteria that should be met in order for a VMP to be authorized/registered. Legislation should establish the various procedural elements required (application process for registration, information and studies to be included in the application, role of competent authority and coordination with other entities, decision making, publication of registration, etc.). The TAHC recommends that procedural rules should favour transparency, stating that legislation should address "the technical, administrative and financial conditions associated with the granting, renewal, refusal and withdrawal of authorizations" (Article 3.4.11).

Legislation may establish the data requirements that need to be submitted in the application dossier, and these commonly include: the name and details of manufacturer, including country of origin and status of registration in that country; ingredients, pharmacology, toxicology; purpose, route of administration, dosage, ADI, side effects, contraindications; shelf life, withdrawal periods, directions for its use, particular hazards; efficacy and other tests and trials conducted and their results; container and package specifications and proposed advertising materials and labelling to be used (Fingleton, 2004). Specifications regarding MRL and other food safety or environmental impact parameters may be required at this stage. For example, in the TAHC this includes information relating to stability when mixed with feed or drinking water, and safety requirements, including potential biological effects on the intestinal flora of humans (Article 6.10.3).

The MRLs should be established, either by the food safety authority alone or together with the authorization/registration authority. Routes of administration and dosages may be influenced by the MRL. The withdrawal period may be used to ensure the MRL is not exceeded. The withdrawal period is the period between the treatment and the slaughter of the animal (or extraction of foods from the animal) to minimize residues of antimicrobials in meat, milk, eggs or other products derived from the treated animal. The *EU Regulation 2019/6* lists the data requirements to be submitted in the application dossier for marketing authorizations. If the product in question is an antimicrobial, the dossier must include, among other information, documentation on the direct or indirect risks to public or animal health, as well as information about risk mitigation measures to limit AMR development related to the use of the VMP (Article 8). Notably, this Regulation requires an environmental risk assessment to be performed to assess the risks of harmful effects on the environment and to identify precautionary measures to reduce such risks.

Transparency is required around the specific decision-making criteria for authorization/registration of a VMP. The process may establish explicit conditions or rules relating to the specific product, relating to packaging, labelling and advertising, in addition to quality standards and production processes. Also, specific rules relating to disposal of the product may be established at this time – including specific waste management aspects related to the disposal of unused or expired VMPs, as well as waste from animals treated with antimicrobials. In fact, data requirements provide an opportunity to include AMR-specific parameters, for example, data on selection for resistance, or whether varying dose ranges or durations of treatment are indicated to minimize the risks of AMR. These factors may be reflected in the approved product labelling. Labels should also be required to include clear indications, directions and warnings that promote the prudent use of VMPs containing antimicrobials.

The *EU Regulation 2019/6* requires that all VMPs, as a condition of marketing, should undergo an environmental risk assessment to assess the potential harmful effects that the use of the product may cause to the environment, and to identify any precautionary measures that may reduce such risks. This involves an evaluation of the possible hazards to the environment posed by a VMP, and as a result, ecotoxicity data is required as part of the safety submission. Also evaluated under this process is the disposal of unused VMPs or their waste products on the environment. No VMP is to be placed on the market without these environmental aspects of safety being determined. Furthermore, the Regulation articulates AMR as one of the parameters in considering whether to grant or refuse marketing authorizations for a VMP. According to Article 37, the competent authority should deny authorizations when the risk to public health from AMR outweighs the benefits of the VMP to animal health, even if the VMP would otherwise fulfil all the requirements, and also where the antimicrobial is reserved for treatment of certain infections in humans. Similarly, in China, the *Examination and Review Criteria for Veterinary Drug Registration (2017)* holds that a registration shall not be granted if there is cross-drug resistance among the compound ingredients of a VMP (Article 15).

It may be opportune for technical data requirements or decision-making criteria to be included in secondary legislation that can be easily updated following scientific developments. The United Republic of Tanzania provides an example where the primary legislation has relatively simple requirements for the registration of VMPs, which are then further elaborated in accompanying guidelines. Under the country's *Food Drugs and Cosmetics Act (2003)*, registration is required for "veterinary pharmaceuticals" prior to their manufacture, sale, supply or import (Section 22). The Tanzania Food and Drugs Authority is responsible for approving registrations when it considers the availability of the specific VMP to be in the public interest, and if it is "*safe, efficacious and of acceptable quality"* in relation to its effect on the health of animals, consumers of food of animal origin, the environment and users (Section 51). The Authority's "*Guidelines on submission of documentation for registration of veterinary medicinal products*" provides more detailed requirements, *inter alia*, drug residues assessment and antibiotic resistance evaluation reports when applying for the registration of a VMP. The application is also required to conform with labelling requirements for the VMP (TFDA, 2016).

The registration process may establish pre-authorization quality control processes. These may include: quality standards for the raw materials as well as the final product; testing for product safety and efficacy; and conducting clinical and non-clinical trials. Clinical trials may be subject to specific authorization requirements. For example, Section 5 of Nigeria's *Food, Drugs and Related Products Act (as amended in 1999)*, requires authorization for clinical tests and compliance with specific rules and procedures.

In summary, the CXC 61-2005 (Sections 9-16), and Article 6.10.3 of the TAHC, indicate that the registration process should include the following elements:

i. the obligation to register VMPs, with exceptions for emergencies and research;
ii. efficient registration procedures that evaluate the quality, safety and efficacy of VMPs containing antimicrobials;
iii. the data necessary for granting marketing authorization and, for this purpose the competent authority should:
    a. assess the risks to animals;
    b. assess the risk to humans resulting from the use of antimicrobials in food producing animals (safety evaluation), taking into consideration:
        i. each individual antimicrobial as well as the class of antimicrobials to which the active ingredient belongs;
        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 antimicrobial or VMP ingredients, in terms of AMR.

The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is a trilateral programme involving the European Union, Japan and the United States. The VICH programme has provided guidelines for the registration of antimicrobial VMPs intended for use in food-producing animals through its *Guidance on Pre-approval information for registration of new veterinary medicinal products for food-producing animals with respect to antimicrobial resistance (Guideline 27)*. These guidelines recognize that when evaluating the antimicrobial safety for use in food-producing animals, regulatory bodies should consider the potential for such products to select for resistant mircoorganisms. The guidelines thus set out the types of studies and data that should be provided to registration bodies to characterize the potential of the product to select for antimicrobial-resistant microorganisms under the proposed conditions of use. The guidelines provide standards for the registration of antimicrobials, which include test data for minimum inhibitory concentration tests, resistance mechanisms and genetics, and the occurrence of resistance and cross-resistance as well as pharmacokinetic data.

Some countries do not have the relevant resources (technical, financial or human), to undertake the requisite assessments themselves. These countries may rely primarily on imports from other countries, but authorizations are still required for VMPs (see Section 7.1.6 for more on import controls). Veterinary legislation may allow also for the recognition of the equivalence of authorizations made by other countries (Article 3.4.11 of the TAHC). In such cases, the competent authorities typically request information on the status of authorizations issued in other countries (Article 6.10.3 of the TAHC and Section 3.1 of the CXC 61-2005). The competent authority may develop a list of pre-authorized countries determined as having a reliable VMP registration system. Essentially this simplified process accepts products that are registered in certain other countries, and based on the information provided, a consideration is made with regard to climatic, geographical, species, dietary or other country-specific aspects which may affect key data points that have been presented in the application. Furthermore, competent authorities may enter into technical cooperation arrangements with authorities of their trading partners to improve capacity to control imported VMPs, as well as the validity of the

recommended conditions of use (Article 6.10.3 of the TAHC and Section 3.1 of the CXC 61-2005). Legislation may place a requirement on the importer or registrant to provide quality certificates prepared by the competent authority of the exporting and manufacturing country as appropriate (Article 6.10.3 of the TAHC).

The CXC 61-2005 and Chapter 6.10 of the TAHC also encompass aspects of regulation of preclinical trials towards ensuring the efficacy of the VMP and to establish an appropriate dosage regimen that ensures efficacy and prohibits AMR development. This is often established at the registration stage. Most countries will not include this level of detail in their primary or even secondary legislation, as these requirements are subject to continuous scientific updates and require flexibility to be updated. For those countries that include requirements for preclinical trials into documents of a legal nature (regulations, technical standards, procedures), it is important to periodically verify their continued alignment with the updated international reference standards. Chapter 3.4 of the TAHC stipulates that veterinary legislation should address the following elements: (i) the conduct of clinical and non-clinical trials to verify all claims made by the manufacturer; (ii) conditions for the conduct of trials; and (iii) qualifications of experts involved in trials.

In accordance with the principles of transparency, the reasons for cancelling registration should also feature in legislation. Section 4 of Nigeria's *Food, Drugs and Related Products Act (as amended in 1999)* calls for suspension or cancellation if: (i) the grounds on which the VMP was registered was false or incomplete; (ii) circumstances leading to registration have changed; (iii) conditions of registration have been breached; (iv) the standards of quality, safety or efficacy are not met; or (v) the premises for the manufacture or storage of the registrant are later found to be unsuitable. The legal consequences of cancelled registration include withdrawal from circulation and the publication of the cancellation in the Gazette (Section 4).

Effects of registration

According to Chapter 3.4 of the TAHC, veterinary legislation should ensure that only authorized/registered VMPs are placed on the market (this includes medicated feed and products prepared by authorized veterinarians or pharmacists). Legislation frequently includes a clear prohibition against putting unregistered VMPs on the market, with limited exceptions for emergencies and research. Nigeria's *Food, Drugs and Related Products Act* stipulates that no drug shall be manufactured, imported, exported, advertised, sold or distributed unless it has been registered in accordance with the law. This type of prohibition has a very strong impact on the market and should be accompanied by appropriate monitoring and enforcement mechanisms. The registration process may also result in rules relating to record-keeping and reporting obligations for sellers, prescribing veterinarians and users.

Approval of authorization/registration should result in the entry of the product into a list or registry of VMPs permitted for use in the country. This list or registry should give the VMP a unique identification number and should indicate how it is classified based on typology and potential hazard. The registry should set out: the species on which the product may be used; the manner of administration; withdrawal periods; the ADI; and storage requirements. This information could be then used to direct livestock owners to use low-hazard products, which contributes to a more diverse market, rather than one dominated by a single product. Information should be entered in the list or registry (and also included in the terms and conditions of any authorization or registration), relating to any restrictions with regard to supply, distribution, and administration of the product.

Once a new product has been authorized or registered, any additional person may apply for a licence to either manufacture, import, distribute or sell that product. Typically, registration of VMPs is considered a "public good" and therefore does not by itself confer sole rights over the drug on the person registered (Fingleton, 2004). Some countries allow for indefinite authorization or registration until circumstances give rise to the need to cancel registration, while other countries allow authorization for a set period to allow for re-evaluation and updated risk assessment based on new information (Fingleton, 2004).

It should be clarified that registration must be distinguished from any patents or other intellectual property rights (IPRs) associated with the product itself. The IPRs are exclusive rights granted to the entity that develops the VMP and helps to support innovation and the creation of products. These exclusive rights are incentives for the entities that typically invest significant sums to finance research and development activities related to the products (see Box 6).

Box 6. Intellectual property rights and the development of new medicines

Intellectual property rights (IPR) regimes should incentivize, rather than restrict, access to veterinary medicinal products (VMPs) and the innovation of new VMPs. Target 3b of the Sustainable Development Goal 3, which serves to "Ensure healthy lives and promote well-being for all at all ages", refers to the *Declaration on the TRIPS Agreement and Public Health (Doha Declaration)*, and calls for countries to:

> "Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration […] which affirms the right of developing countries to use to the full the provisions in the TRIPs Agreement regarding flexibilities to protect public health, and, in particular, provide access to medicines for all."

The Doha Declaration recognizes that "intellectual property protection is important for the development of new medicines", while also warning about IPRs' potential effects on prices (WIPO, WHO and WTO, 2020). The Doha Declaration confirms that the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) can and should be interpreted and implemented in a manner supportive of World Trade Organization (WTO) Members' rights to protect public health and to promote access to medicines for all. The Doha Declaration reaffirms that the TRIPS Agreement provides 'flexibilities' for this purpose. While the TRIPS Agreement has not formally defined the exact meaning of "flexibilities" (WIPO, WHO and WTO, 2020), the term is understood to include the ability to issue compulsory licences, authorize parallel importation, apply general exceptions, and employ competition laws to limit and remedy the abuse of IPR in domestic legislation (UNHLP, 2016).

The Doha Declaration led to the amendment of the TRIPS Agreement in 2017, by the introduction of Article 31bis on a Special Compulsory Licensing System. The Article provides the basis for WTO members to grant special compulsory licences exclusively for the production and export of affordable generic medicines to other members that cannot domestically produce the needed medicines in sufficient quantities for their patients. This additional flexibility is designed to help countries with insufficient or no manufacturing capacities in the pharmaceutical sector to make effective use of compulsory licensing (WIPO, WHO and WTO, 2020).

Sources: WIPO (World Intellectual Property Organization), WHO & WTO (World Trade Organization). 2020. *Promoting Access to Medical Technologies and Innovation - Intersections between Public Health, Intellectual Property and Trade*. Geneva, Switzerland, World Intellectual Property.

UNHLP. 2016. *Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines - Promoting innovation and access to health technologies*. https://www.unsgaccessmeds.org/s/UNSG-HLPReport-FINAL-12-Sept-2016.pdf

It should be noted that quality control begins during the registration process and continues after registration. Legislation should also prescribe how quality standards are set (often during registration by the competent authority) and monitored/enforced (often through inspections at all stages of production and distribution, and also through self-audit/self-testing undertaken by the manufacturer).

Categorization/classification

At the time of registration, a VMP may be classified in a designated category which does not refer to pharmacological classes, but instead to the means of dispensing the VMP. Countries may include all (or various combinations) of the following classes: (i) prescription only; (ii) pharmacy; (iii) authorized dealer; and (iv) general sale.

On this spectrum of distributors, those under class (i) can issue all types of VMPs, while those under class (iv) can only issue VMPs that are classified as general sale. An example of such categorization is offered in Box 7. Legislation should define any terms used in connection with classification; for example, in Box 7, terms such as veterinarian or authorized dealer that may appear in the law should be defined. Box 7 categorizations are for illustrated purposes only, and various combinations can be used in a country. What is important for regulators to note is that classifications should be formulated in a way that allows varying restrictions in dispensation of VMPs, where required.

Box 7. Examples of veterinary medical products categorization/classification

Prescription only	Pharmacy	Authorized dealer	General sale
Veterinary drugs subject to restrictions on supply and use based on international conventions, or on special precautions to avoid unnecessary risks or on the necessity for precise diagnosis.	Veterinary drugs which require advice to be given regarding potential risks, undesirable interactions, method of use or conditions of storage or safe disposal.	Veterinary drugs not suitable for general sale.	Any other veterinary drug.
Restrictions: Such veterinary drugs may only be sold to the public by a veterinarian or a pharmacist, and only in accordance with a written prescription of a veterinarian.	**Restrictions:** Such veterinary drugs may only be sold to the public by a veterinarian, a pharmacist or a licensed dealer.	**Restrictions:** Such veterinary drugs may only be sold to the public by a veterinarian, a pharmacist, a licensed dealer or an authorized dealer, and only in unbroken packages as prepared by the manufacturer.	**Restrictions:** Such veterinary drugs may be sold by any person or establishment, in unbroken packages as prepared by the manufacturer.

Source: Fingleton, J. 2004. *Legislation for veterinary drugs control.* FAO Legal Papers 38. Rome, FAO. http://www.fao.org/3/a-bb071e.pdf

The *EU Regulation 2019/6* establishes a classification of VMPs in Article 34 and provides for the grounds under which a VMP must be subject to a prescription, and where it can be sold without a prescription. Notably, Article 34(1c) explicitly lists antimicrobial VMPs as requiring a prescription.

Whatever the categories created, the law should consider VMP availability and access, having regard to the nature of the product, and the degree to which certain retailers or dispensers can make VMPs available where required. The classification process requires a balance to be struck between the goal of ensuring only skilled personnel prescribe or administer the VMP (so that it is used in the most prudent manner) and the goal of making the VMP available broadly in the country, including in remote regions where farms may be located. Among the aspects to consider in making such determinations are: (i) availability and access to VMPs in the country (manufacture, import, prescription, sale/dispensing); (ii) when the VMP can be used; (iii) for what purpose the VMP will be used; (iv) who can access the VMP; and (v) criteria for use of the VMP.

Formulating a national list of essential veterinary medicines and the WOAH List of Antimicrobial Agents of Veterinary Importance

Separate to the list or registry of authorized or registered products, the competent authorities may develop a list of essential veterinary medicinal products. Priority for registration may be given to VMPs considered important, based on a country's particular livestock needs and circumstances (Fingleton, 2004). This national list may be based, as regards antimicrobials, on the WOAH *List of Antimicrobial Agents of Veterinary Importance*. The WOAH List includes all antimicrobial agents authorized/registered for use in food-producing animals (while excluding those used only for human medicine or as growth-promoters) and categorizes them as either Veterinary Critically Important Antimicrobial Agents, Veterinary Highly Important Antimicrobial Agents or Veterinary Important Antimicrobial Agents.

The legal framework (typically public health laws) may require however, that antimicrobials listed for use in humans be used exclusively for humans. Therefore, it is important that VMP legislation is consistent with public health laws. For example, under *EU Regulation 2019/6*, the European Commission is empowered to designate antimicrobials reserved only for treatment of certain infections in humans. No VMP authorization can be given for an antimicrobial placed on this list (Article 37). Alternatively, such provisions could be found in veterinary legislation. Cabo Verde's *Law No. 30/VIII/2013 establishing veterinary safety norms, animal health and environmental safety for animal origin products* prohibits veterinarians or veterinary technicians from prescribing to an animal any medicine designated for human use. Kenya's *Veterinary Surgeons and Veterinary Paraprofessionals (Veterinary Medicines Directorate) Regulations (No. 209 of 2015)* establishes a penalty for anyone who supplies human medicine for administration to an animal.

WHO has developed a *List of Critically Important Antimicrobials for Human Medicine*, which is essentially a classification of medically important antimicrobials. The WHO List supports risk assessment and risk management of antimicrobial use in food-producing animals by facilitating an understanding of which antimicrobials used in the veterinary sector pose higher AMR risks to humans (WHO, 2017a). The WHO List is supported by the *WHO Guidelines on Use of Medically Important Antimicrobials in Food-Producing Animals*, which present evidence-based recommendations and best practice statements on the use of medically important antimicrobials in food-producing animals (WHO, 2017b). In combination, the WOAH List and the WHO List allow for risk management and considerations of animal health, human medicine and agriculture under a coordinated One Health approach (WHO, 2017a).

7.1.6. Import

Overview of key regulatory elements for imports

- Import permits and inspections frameworks that target key risks and facilitate trade help to prevent challenges relating to the entry of substandard, falsified, unregistered VMPs in the country.

Rationale

Many countries source their VMPs from outside their territory. These countries are at particular risk of substandard, falsified, unregistered and even banned VMPs flooding the domestic market – more so where countries have porous borders and inadequate import controls. Illegal and uncontrolled imports limit the ability of authorities to manage data on quantity and quality of VMPs in the country. Illegally imported products may not be registered, and thus, VMPs that are unsafe or of poor quality circulate freely

in the country. This is worsened by the lack of restrictions in prescriptions, without the necessary labelling instructions or warnings to guide use, and without other controls that promote their safe and prudent use.

Requirements

Importers are usually required by law to obtain an import permit or approval from the competent authority (in addition to other approvals as may be required by customs legislation) to bring VMPs into the country. Usually, such a permit is granted for a specified duration where an applicant meets prescribed conditions, and where the application fee is paid. Applications for import would only be approved where the VMP is authorized or registered and appears on the official list or registry for acceptable VMPs. Import authorization systems may sometimes combine the authorization of the operator, and the product import, under the same administrative process. For example, this method may be used for regular periodic imports, in such a manner as would facilitate trade and remove the need for fresh permit applications for individual consignments. Importer requirements typically include record-keeping and reporting on the types and amounts of VMPs imported, as well as reporting to ensure compliance with the safe storage and handling of VMPs.

An import control system that is risk-based will focus resources for inspections and monitoring on products (or importers), which are demonstrated to pose a risk higher than what is considered acceptable to the importing country. Samples may be taken during the importing process where verifications can be made regarding the product characteristics. Some packaging and labelling rules relate specifically to imports, such as language specifications or other country-specific requirements. Inspections will also verify whether the product bears the prescribed information on its label. It should be noted that some countries explicitly exclude small quantities that are brought into the country for self-consumption from import controls.

In the United Kingdom, the import of authorized VMPs is governed by the *Veterinary Medicines Regulations (2013)*. According to the Regulations, the holders of either a marketing or manufacturing authorization may import the VMP to which their authorization relates. Authorized wholesale dealers may also import VMPs where they have notified the holder of the marketing authorization in writing prior to importation. Importantly, veterinary surgeons or pharmacists may also import any authorized VMP. Suitably qualified persons, registered in accordance with the Regulations, may also import VMPs that such persons are permitted to supply. Finally, there are no restrictions on the import of authorized VMPs for medicines classified as "over-the-counter" (Article 9). China's *Administrative Measures for the Import of Veterinary Drugs* (2007) requires the import of VMPs to take place through ports where the competent authority has inspection capabilities in place (Article 4). Importation of VMPs requires, among other factors, the importer to be in a possession of: (i) a "veterinary drug production licence"; (ii) manufacturing inspection reports; (iii) a copy of the Chinese label; and (iv) manual of use for the product (Article 5).

7.1.7. Manufacturing

Overview of key regulatory elements for the manufacturing of veterinary medicinal products

- Manufacturing controls should focus on quality, safety and efficacy.
- Whether manufactured separately or in combination with human medicines, there should be a system of authorization (permits/licensing) for veterinary medicinal products (VMP) manufacturers enforced by a system of inspections.
- Manufacturers should be legally required to keep prescribed records relating to VMP production.
- Environmental impacts may be mitigated through adherence to good manufacturing practices (GMPs), the duty to submit an Environmental Impact Assessment as a condition of applying for a licence, and obligations relating to waste treatment and disposal.

Rationale

Controls over the manufacturing stages of the VMP lifecycle seek to ensure the safety, quality and efficacy of VMPs (finished product and active pharmaceutical ingredient) that are manufactured. Also relevant, particularly for AMR, is that controls over manufacturing seek to ensure the safe disposal of waste and to prevent the release of antimicrobials into the environment.

Requirements

The operation of manufacturing facilities for the production of VMPs may require permits or approvals from various competent authorities that are responsible for: veterinary matters, human health and medicine, environmental authorities, local authorities and business/industry/commerce authorities, among others. The CXC 61-2005 (Section 17) and the TAHC (Chapters 6.10 and 3.4) provide overall guidance on regulating the manufacture of VMPs, including adherence to good manufacturing practices (GMPs).

The first regulatory issue here is whether or not such facilities are also (or exclusively) subject to rules pertaining to the manufacture of human medicines. Manufacturers may produce drugs for both human and animal use, and often these may be the same products. In such cases, the applicable regulatory rules and requirements that should be followed by operators of a facility should be clear enough for compliance and implementation by the operator, and the controls carried out by regulatory authorities should not be duplicative. A factory may be licensed under legislation for human health but may require an additional permit to produce VMPs. Such a permit should elaborate which specific VMPs can be manufactured, for how long the permit is valid, and any applicable terms and conditions. Such a permit can provide an avenue by which to introduce specific additional or specific quality standards.

Permit or licensing systems are usually accompanied by a framework for inspections. Legislation may require manufacturers to facilitate inspections and may require self-assessment or self-audit practices. Legislation may impose the duty to keep prescribed records of their operations. Record-keeping contributes to the collection of accurate data on the amounts of antimicrobials entering the market. In Norway, under the *Medicines Act (as amended in 2018)*, manufacturers must have a manufacturing licence before their VMP can receive marketing authorization. Egypt's legislation is brief but contains the principal elements; the *Ministerial Decree No. 673 of 2011 on the licensing of factories producing veterinary products* sets out a scheme for licensing as well as quality assessment certification and follow-up inspections.

Facilities should be required to meet specific conditions relating to construction and should be under the supervision of a qualified technician. Legislation may require the manufacturer to appoint a person who meets the prescribed qualification requirements as responsible for the manufacturing operations, record-keeping, etc. Japan requires a licence for manufacturing pharmaceuticals, including those that manufacture veterinary pharmaceuticals under Article 13 of the *Act No. 145 on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (as last amended in 2015)*. To ensure the appropriate expertise in the manufacturing process, Article 17 also requires that a manufacturer of pharmaceuticals appoints a pharmacist for each manufacturing facility to manage the manufacturing of pharmaceuticals on site.

Legislation may require the adoption or application of good practices by manufacturers, i.e. GMPs and good storage and distribution practices, including good cold chain management practices, collectively referred to as GXP. The GXP contribute to ensuring the quality, safety, and effectiveness of VMPs. Canada, under the *Food and Drug Regulations (C.R.C., c. 870, as last amended in 2020*), requires the manufacturing of active pharmaceutical ingredients, which includes those used in antimicrobials, to follow the good manufacturing practices established in the Regulations (C.02.003.3). In China, as per the *Regulation on*

veterinary drug administration (2016), conditions for a licence to manufacture include having personnel, instruments and equipments that meet prescribed requirements for management and quality control functions, a manufacturing environment that meets safety and sanitation requirements (e.g. GMPs), as well as other production conditions stipulated in the veterinary production quality management regulations.

These GMP systems also ensure that environmental impacts are mitigated. The WHO *Good manufacturing practices for pharmaceutical products containing hazardous substances* (2010) for example, contains guidance on the management of waste and wastewater. Additionally, EIAs are often a pre-condition for the issuance of a licence (referenced either in VMP laws, manufacturing laws or environmental laws). An EIA enables a determination to be made on the impacts of a manufacturing facility on the surrounding areas (see Section 8.2.8 of this Study). The GMP systems may also complete environmental legal obligations relating to pollution and the discharge of waste. A VMP legislation may contain a reference to such environmental laws or may specifically reference the duty to minimize environmental contamination. An example of the latter is the duty to set up waste treatment mechanisms to prevent the discharge or dispersal of antimicrobials into the environment.

The CXC 61-2005 and Chapter 6.10 of the TAHC highlight the following elements for VMP quality control regulation: (i) basing production on GMP; (ii) ensuring that the quality and concentration (stability) in the marketed dosage form is maintained and properly stored up to the expiry date under the recommended storage conditions; (iii) ensuring the stability of VMPs when they are mixed with feed or drinking water; (iv) ensuring that the antimicrobial agents and the VMPs containing them are manufactured to the appropriate quality and purity to guarantee their safety and efficacy; and (v) verifying that the analysis specifications of antimicrobial agents used as active ingredients for VMPs comply with the registration documentation requirements.

Quality controls include verifying the quality of VMP raw materials, the composition of VMPs as well as safety and efficacy testing. Quality control at the manufacturing stage may entail a requirement to apply a GMP and receive appropriate certification, as well as a duty on the manufacturer to establish and record quality assurance systems that incorporate tests on raw materials and the final product. Regulatory authorities may find value in the Pharmaceutical Inspection Co-operation Scheme,[7] which is a non-binding, informal co-operative arrangement between regulatory authorities in the field of GMPs of medicinal products for human or veterinary use. Retailers and other points of sale have an obligation to stock only authorized VMPs in addition to the duty to ensure prescribed cold chain and other storage practices where required. Importers and manufacturers may be required to recall VMPs that do not meet prescribed quality standards. In the United Kingdom, under the Second Schedule of the *Veterinary Medicines Regulations (2013)*, a holder of a manufacturing authorization has the following obligations, among others: ensuring that the VMPs are manufactured as per the marketing authorization; possess a valid Certificate of GMP; have in place a system of quality assurance and quality control; and submit to the relevant authority proof of all control tests carried out on the VMP or its constituents and intermediate products. Where the manufacturer is in compliance with the principles and guidelines on GMP in accordance with the European Union's *Commission Directive 91/412/EEC*, the competent authority will issue a certificate of GMP to the manufacturer. The European Union's *Directive 2011/62/EU on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products* stipulates the duty to use obligatory safety features which form part of its framework for quality control to prevent substandard and falsified medicines; these features include unique identifiers and anti-tampering devices on the outer packaging of medicines (Article 52). The Directive creates rules on the import of active pharmaceutical ingredients (Article 46b) and record-keeping obligations for wholesale distributors (Article 80).

7 See PIC/S, 2023.

7.1.8. Quality control: a focus on substandard and falsified veterinary medicinal products

Overview of key regulatory elements for quality control of veterinary medicinal products

- Quality control provisions can be found at different stages of the veterinary medicinal products (VMP) lifecycle – at registration, manufacturing and distribution.
- Legislation should:
  - establish clear definitions of substandard and falsified VMPs;
  - make it an offence to manufacture, import, sell or otherwise deal in substandard or falsified VMPs.
- Legislation should establish a system for the identification of VMPs and recall/withdrawal from the market of substandard or falsified VMPs.

Rationale

Substandard and falsified products represent a local and a global health problem and concerns the integrity of the manufacturing and supply chain. These types of products create a number of serious risks: the product may be unsafe for use; the product may lack efficacy in treatment; higher doses or quantities may be required; or animals may be left unprotected from disease. These types of products can also contribute to build-up in resistance in both animals and humans. According to WHO (2017c), there are three main factors fuelling the creation of falsified and substandard products: (i) high prices of medicine; (ii) inadequate access to affordable medicines; and (iii) drug shortages. The possibility of charging high prices creates a profit motive for unscrupulous manufacturers, while inadequate access to affordable medicines and VMPs create the demand and market. Quality controls prevent substandard and falsified antimicrobials from entering the market.

Definitions

WHO has defined what is considered "substandard", "unregistered" and "falsified" in the context of the WHO global surveillance and monitoring system. These definitions are created for "medical products", which is a concept wide enough to cover both human medicines and VMPs. These definitions replace older classifications, including "spurious", "falsely-labelled" and "counterfeit". Box 8 shows the WHO definitions for substandard, unregistered and falsified medical products.

Box 8. WHO Classification of Medical Products

A medical product includes: "medicines, vaccines, *in vitro* diagnostics, medical devices (including immunization devices), cold chain equipment, vector control products, blood products, sera, anti-venoms, monoclonal and other biotherapeutic products (including similar biotherapeutic products)".

SUBSTANDARD	UNREGISTERED	FALSIFIED
Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or their specifications, or both.	Medical products that have not undergone evaluation or approval by the competent authority for the market in which they are marketed or used, subject to permitted conditions under national or regional legislation.	Medical products that deliberately/fraudulently misrepresent their identity, composition or source.

Source: WHO. 2017c. *Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products*. Report by the Director-General. Seventieth World Health Assembly. A70/23. 36 pp. https://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf

Intellectual property rights considerations are explicitly excluded from the definition of *falsified medical products*. Rather, *in a WHO report from 2017,* the latter category refers to any substitution, adulteration, or reproduction of an authorized medical product or the manufacture of a medical product that is not an authorized product (WHO, 2017c). The report also gives guidance on the three defining features of "identity", "composition" and "source". According to WHO, identity refers to the "name, labelling or packaging or to documents that support the authenticity of an authorized medical product"; composition refers to any "ingredient or component of the medical product in accordance with applicable specifications authorized/ recognized by [national and/or regional regulatory authorities]"; and source refers to the "identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter distributor or retailer, as applicable" (WHO, 2017c, p.35).

The WHO report (2017c) also recognizes that the term "counterfeit" is defined and associated with the protection of intellectual property rights but it stops short of providing a definition for "counterfeit medicine" or "counterfeit medical product". In the absence of a WHO definition, the definition for "counterfeit medicine" adopted by the European Medicines Agency (EMA) may prove enlightening: "a medicine made by someone other than the genuine manufacturer, by copying or imitating an original product without authority or rights. Counterfeit medicines infringe trademark law" (EMA, 2020).

Controls

While parts of VMP quality aspects may be addressed in VMP-specific legislation, some aspects of the quality control of products may be included in general consumer protection legislation. Regulators should understand which institutions have a mandate in controlling substandard or falsified products. While the entity in charge of implementing VMP legislation may have such a mandate, others such as local authorities or authorities responsible for consumer protection or fraud may also have a legally mandated role. Regulators should thus coordinate to maximize use of available resources and to leverage the strategic strengths of various bodies in enforcement.

Many aspects of quality control take place at the sale and distribution stage. A risk-based system that comprises inspections and sampling campaigns may be used to verify the quality of antimicrobials at different points in the VMP lifecycle. Risk-based strategies will target, for example, food producing animals, certain types of antimicrobials (e.g. antibiotics), and biologicals for notifiable diseases or zoonoses that have been detected in the country. Cooperation with the authorities responsible for consumer protection will provide an additional arsenal of enforcement mechanisms to maximize use of available resources. Legislation may empower inspectors to target points of sale and distributors. Under the Second Schedule of the United Kingdom's *Veterinary Medicines Regulations (2013)*, the competent authority bases the frequency of inspections on the risks associated with each premises, allowing a development of a historical risk profile, which is also based on the nature of the products handled.

Legislation typically empowers inspectors to carry out a range of inspection activities for the purposes of quality control, including sampling and testing of VMPs offered for sale, as well as seizure of goods suspected as being substandard or falsified. Whether through mistake, incompetence or malice, not all marketed VMPs meet the legally established quality standards. Placing substandard, falsified or counterfeit VMPs on the market is often stipulated as an offence in legislation, which attracts a range of administrative and criminal penalties. Thailand's *Drug Act B.E. 2510*, prohibits the production, sale and import of fake, substandard, deteriorated and non-registered drugs (Section 72). The Act also defines fake drugs as those which are, either wholly or partly, an imitation of a genuine drug, a drug that shows the producer's name or location of another drug, or a drug that has a false expiry date. Also included are products that falsely show adherence to a registered formula, or drugs with active substances of quantity or strength lower than the mandated amount by more than twenty percent (Section 73).

Legislation should include a provision on the designation of official laboratories (either public or private, within or outside the country) to test VMPs for quality and efficacy in order to identify substandard, adulterated or falsified products. Zambia's *Medicines and Allied Substances Act* (*No. 3 of 2013)* established a National Drug Quality Control Laboratory to verify the safety, quality and efficacy of medicines (including VMPs) (Section 54). Analysts are required to analyse samples as soon as received, and to issue a certificate of analysis. In addition, the Zambia Medicines Regulatory Authority is also empowered to send samples to any other approved laboratory for the purposes of the Act. Legislation may require the adoption of good laboratory practices (GLP). Japan's *Notification on the Good Laboratory Practice for Agricultural Chemicals (No. 11 of 1999)* sets out GLP for labs testing samples for registration.

In addition to the quality control measures discussed in the preceding section, legislative provisions on marketing authorization and a range of GXPs (e.g. good manufacturing practice, good distribution practice, good pharmacy practice, good pharmacovigilance practice, good importation practice and good clinical practice) are all aimed at preventing substandard and falsified VMPs. An essential part of this framework is to ensure that only authorized and licensed supply chain stakeholders are involved in VMP transactions (WHO, 2017c).

7.1.9. Labelling, packaging and advertising of veterinary medicinal products

Overview of key regulatory elements for labelling, packaging and advertising of veterinary medicinal products

- **Veterinary medicinal products** (VMPs) should not be sold or distributed without labels and packages that comply with the law.
- Labels on VMPs should be consistent with the marketing authorization as follows:
  - be in the local or official (or commonly used) language;
  - contain information on dosage and treatment duration, with specific directions in the case of antimicrobials;
  - contain clearly visible use instructions and safety warnings.
- Packaging should prevent the degradation of VMPs under regular conditions of storage and use.
- Advertisements and health claims should not be deceptive or misleading and should be compatible with the principles of responsible and prudent use.
- Advertising of antimicrobials should target only those who are authorized to issue prescriptions for the antimicrobial.

Rationale

Establishing the required information and details to display on the label of a VMP product, is a means to ensure the safe administration, storage and use of a VMP, particularly antimicrobials. Packaging, which refers to the container and protective wrapping around the substance may affect the efficacy or safety of the VMP, which therefore has implications for AMR. Advertising of VMPs is controlled to ensure that the content of publicity campaigns or health claims comply with the approved authorization/registration.

Labelling

Legislation should stipulate that VMPs may only be sold or distributed bearing a label displaying the required information (noting that particular parameters or considerations regarding labelling may be made during registration). Inspections of labels typically form part of broader inspection, monitoring and surveillance

schemes for enforcement. Such generic requirements to be included in legislation may stipulate that labels are written in a local or official language to ensure users can understand it. Under Section 9 of Ethiopia's *Veterinary Drug and Feed Administration and Control Proclamation (No. 728/2011)*, no person may distribute or dispense a VMP which does not bear a label, and labels are to be written in either Amharic or English and include the words "for veterinary use only". Canada in the *Food and Drug Regulations (C.R.C., c. 870)* has specific rules for the labelling of antibiotics for parenteral use that are recommended for veterinary use only. Under the Regulations, the inner and outer labels of such products should indicate the potency of the drug and the statement "For Veterinary Use Only" or "Veterinary Use Only" (C.01.605).

Parameters for labelling may require the inclusion of serial numbers or authentication marks that prevent the circulation of unregistered or falsified VMPs on the market. It may be stipulated that labels require information on dosage and treatment duration, which is especially important in the case of antimicrobials to minimize AMR development. Labels should also contain clearly visible instructions for use and appropriate safety warnings. In Norway, under the *Medicines Regulation (2009)*, the competent authority must approve the labelling of a VMP when granting a marketing authorization (Section 3–29). A VMP shares the same labelling requirements as medicines for human use (Section 3–29). However, additional requirements for VMPs include: that the label identifies what animal species the drug is intended for; the withdrawal period for VMPs that are fed to food-producing animals; the worded inscription "for animals"; and for prescription drugs, the worded inscription "prescription" in Norwegian (Section 3-30). In China, the *Measures for the administration of veterinary drug labels and instructions (2002)* contains the basic requirements for labelling; at minimum the inner label should indicate the veterinary logo, name of the veterinary drug, the function of the veterinary drug, the content/package specifications and the approval document (Article 5), while in addition the outer label is to include information such as the main ingredients, guidance on the usage and dosage of the veterinary drug as well as its expiration date and guidance for disposal (Article 6). The country's *Detailed rules for the preparation of veterinary drug labels and instructions (2003)* specifically considers antibiotic preparations, in which case, labels are to include all effective ingredients and contents (Article 11).

A label may also include a summary of product characteristics necessary for the appropriate use of VMPs. This summary may contain any of the following information, as guided by the 2021 version of the CXC 61-2005 (Sections 9–16) and the TAHC (Article 6.10.3), as follows: active ingredient and class; pharmacological properties and any potential adverse effects; 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 unused or out-of-date products; information on conditions of use relevant to the potential for selection of resistance (for the purpose of guidance on prudent use); and contraindications.

Packaging

Legislative rules for packaging include the requirement that the package should not degrade under normal conditions of storage and use and should not resemble packaging for common consumer goods. Legislation may also include provisions restricting re-packaging of VMPs to prevent expired VMPs being placed on the market. In Australia, when the competent authority considers the registration of a VMP, the suggested specifications for containers for the VMP are a criterion for making a determination as to whether the VMP meets safety criteria (Section 5A(3) of the *Agricultural and Veterinary Chemicals Code Act 1994, Compilation No, 29 (2016))*. The competent authority is also empowered to create standards for containers containing VMPs (Section 8U(4)(b)).

Advertising

The (health) claims made on VMP packaging should be kept to a minimal to include only what is necessary, focus on the medical purpose, and provide instructions for use. These claims and any advertising material

must avoid misleading the user and avoid advertising off-label uses. Article 6.10.3, Paragraph 10 of the TAHC clarifies that: "all advertising of antimicrobial agents should be compatible with the principles of responsible and prudent use and should be controlled by codes of advertising standards. The relevant authorities must ensure that the advertising of these products: (a) complies with the marketing authorisation granted, in particular regarding the content of the summary of product characteristics; (b) is restricted to a veterinarian or other suitably trained person authorised to prescribe VMP containing antimicrobial agents in accordance with the national legislation and under the supervision of a veterinarian."

Norway, under the *Medicines Regulation (2009)*, requires the advertising for VMPs to be serious and factual, and should promote the rational use of the VMP. Health claims and advertising must not give a misleading or exaggerated picture of the properties and medicinal value of the VMP. The advertisement must not lead to the use of the drug which is not medically justified and must be in accordance with the special drug prescription approved by the Norwegian Medicines Agency (Section 13-4). Only non-prescription drugs can be advertised to the public, and considering that all antimicrobial VMPs require prescriptions, these cannot be advertised to the public (Section 13-5). In the *EU Regulation 2019/6*, the advertising of VMPs that are subject to veterinary prescriptions is only allowed when made exclusively to veterinarians or persons permitted to supply VMPs under national law (Article 119). This can be extended to professional keepers of animals, as long as the advertising is limited to immunological VMPs, and the advertising includes an express invitation to consult the veterinarian about the VMP (Article 120). Under Zambia's *Medicines and Allied Substances Act (No 3 of 2013),* medicines (including VMPs) may not be advertised in a manner that is false, misleading or deceptive in respect of its "character, constitution, value, potency, quality, composition, merit or safety" (Section 61). Furthermore, ads must conform to the approved product information specified in the marketing authorization (Section 45). Any person who contravenes these provisions commits an offence under the Act (Section 45).

In some countries, VMP manufacturers and distributors may be prohibited from providing incentives (including bonuses or in-kind benefits) to prescribers or retailers to promote or sell VMPs containing antimicrobials and from supplying free product samples.

7.1.10. Prescriptions

Overview of key regulatory elements for prescriptions

- Legislation should stipulate that the sale or dispensing of certain classes of antimicrobials should be subject to a prescription by a veterinary professional or an equivalent person with relevant training approved in the country concerned.
- The veterinary professional categories that are authorized to issue different classes of antimicrobials should be established by law including their minimum education requirements. Their responsibilities and requirements for continued professional training (e.g. on antimicrobial use) may be found either in the law or in a Code of Conduct.
- Veterinary professionals:
  - are accountable for their antimicrobial prescriptions;
  - may only prescribe antimicrobials for animals under their care;
  - have a duty to keep records and report information on prescriptions to the competent authority;
  - may be legally obliged to adhere to certain antimicrobial use practices.
- The competent authority (or the veterinary statutory body where this exists) has the power to request antimicrobial-related information from all veterinary professionals (public and private).

Rationale

Prescriptions enable veterinary oversight in the use of antimicrobials (thus promoting prudent and responsible use) and ensure accountability in dispensation of these substances. The data collected on prescription and use patterns may be used to inform future policies and interventions. By requiring prescriptions for certain antimicrobials, qualified veterinary professionals (for the purposes of this section, this means veterinarians and other qualified professionals authorized to prescribe VMPs under supervision of a veterinarian) can then be the responsible parties for making the decisions on *when* antimicrobials are used, and *how* antimicrobials are used.

Requirements

All VMPs are classified at the time of their registration to indicate the restrictions applicable to their prescription and dispensing. According to the TAHC, VMPs should only be supplied through licensed or authorized distribution systems and administered by a veterinarian or under the supervision of a veterinarian or other authorized person (Article 6.10.3). Cabo Verde's *Law No. 30/VIII/2013 establishing veterinary safety norms, animal health and environmental safety for animal origin products* identifies the issuance of prescriptions to be the sole authority of veterinarians and veterinary technicians practicing under the supervision of a veterinarian (Article 31). This Law also establishes a List of Veterinary Medicines, comprising those that can be bought with a prescription from a veterinarian or authorized veterinary technician, or those that can be bought without (Article 29). In Ecuador, under the *AGROCALIDAD Resolution (No. 0018 of 2016)*, VMPs are classified in three different groups for the purpose of prescription and marketing. The classification is based on the level of risk to animal health as well as the possible impact on consumer health. Group 1 comprises veterinary psychotropics, narcotics, anabolic products and other products that can: lead to misuses or abuse; have significant toxicity risk for animal health; and create residue risks in animal products and by-products. These are subject to restricted prescriptions and more stringent administrative requirements than for a regular prescription. Group 2 VMPs can only be sold on the basis of a prescription from a veterinarian. This group includes veterinary products with physical-chemical substances, including therapeutic antibiotics, antivirals, etc. Group 3 VMPs can be sold without prescription and includes products which carry no risks when used according to their instructions.

As a general rule, antimicrobials should not be sold or used in the absence of a prescription by a qualified veterinarian. However, where expressly authorized by the veterinary statutory body (VSB) – see Section 9.2 of this Study – a qualified veterinary paraprofessional who is permitted to issue antimicrobials and is under the supervision of a veterinarian (Article 6.10.3 of the TAHC) may administer or prescribe an antimicrobial. The VSB may extend the function of issuing prescriptions beyond veterinarians to veterinary paraprofessionals owing to a shortage of qualified veterinarians that are able to cover the full territory of a country. Such an approach can be seen in Tanzania's *Pharmacy Act (2011),* which applies to a broad category of health professionals, but which allows only prescribed practitioners, including veterinarians, or "any other person as the Minister [responsible for public health] may by Order published in the Gazette, specify" to dispense prescriptions for medicines (Section 39). Ethiopia's *Veterinary Drug and Feed Administration and Control Proclamation (No. 728 of 2011)* establishes a framework for prescriptions. Veterinary drugs can only be prescribed by a veterinarian, following standard prescription procedures and on specified prescription paper. The competent authority may, by directive, issue the list of VMPs that may also be prescribed by animal health professionals as well as those which may be dispensed without prescriptions.

An enumeration of veterinarian responsibilities may be found in VMP legislation, animal health laws, or legislation governing veterinary professionals (or establishing VSBs). Specifics may be spelled out in a Code of Conduct that is binding on veterinary professionals. Regardless of where such responsibilities are located, provisions should make clear that veterinary professionals are the only ones with the authority, responsibility

and accountability to prescribe, or to supervise the prescription of, specified antimicrobials. Prescriptions should be made only for animals under the direct care of a veterinary professional (FAO and WHO, 2015).[8] Antimicrobials that are subject to prescription must only be sold in pharmacies or restricted sales points that are authorized to do so. Medicinal compounding by veterinarians should also be regulated. Under the *EU Regulation 2019/6*, prescriptions are required for a variety of VMPs, including VMPs for food-producing animals and antimicrobial VMPs (Article 34). Article 105 further regulates that a veterinary prescription shall only be issued after a clinical examination, or after any other proper assessment, of the health status of the animal by a veterinarian. Exceptionally, national laws may grant other qualified professionals to issue a veterinary prescription. The VMPs where a diagnosis by a veterinarian is necessary, do not fall within this exempted class. In all cases, the quantity of the medicinal products prescribed shall be limited to the amount required for the treatment or therapy concerned (Article 105). In Norway, under the *Medicines Regulation (2009)*, prior to granting a marketing authorization, the competent authority is tasked with determining whether the VMP should be subject to prescription, and if applicable, which prescription group it should be placed in – A to C with increasingly stringent requirements for their prescription. The criteria for choosing the prescription group involves whether the VMP: (a) needs the involvement of a veterinarian or fish health biologist to control efficacy or adverse effects; (b) directly or indirectly may pose a health risk if misused; (c) has not been fully evaluated for effects or side effects; (d) is intended for parenteral use; or (e) is a new VMP with active substances that have been approved for use in animals for less than five years. The VMPs for food-producing animals would always require a prescription (Sections 7-1 to 7-5). Regardless of the prescription classification, only qualified veterinarians can request prescription drugs for animals under Section 17 of the Norwegian *Animal Health Staff Act (2001)*.

The law should establish a duty on veterinary professionals to monitor, record and report on all prescriptions of specified antimicrobials to the competent authorities in the required manner. Furthermore, veterinary professionals may also have the duty to report on adverse or abnormal effects of the antimicrobial. The competent authority (or the VSB) may have the power to request antimicrobials-related information from all veterinary professionals (public and private) at any time. This facilitates veterinary oversight and provides a basis for benchmarking usage levels on farms, prescription patterns and pharmacovigilance. Laws regulating the veterinary profession may include provisions on veterinary school curricula and require that appropriate attention is paid to AMR and the prudent use of antimicrobials.

7.1.11. Sale

Overview of key regulatory elements relating to sales

- The sale of unlabelled, unregistered, substandard or falsified VMPs should be prohibited.
- Legislation should set out clear offences and penalties regarding the sales of illicit VMPs.
- The locations (types of retailer/outlet) at which certain classes of antimicrobials may be sold or dispensed should be based on the VMP classification at registration and outlined in legislation.
- If veterinarians are permitted to sell VMPs directly, there should be provisions to prevent conflicts of interest.
- All establishments that sell VMPs may be required to keep records on the sale of VMPs; legislation may prescribe specific data requirements.
- The law may also establish a mandatory recall system to withdraw from sale the specific lots of VMPs found (or suspected) to be falsified, substandard or expired.

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

Rationale

Antimicrobial resistance may proliferate as a result of unregulated sales of antimicrobials. As noted in Section 7.1.8, unlabelled, unregistered, substandard or falsified VMPs may be unsafe for use, result in ineffective treatment (thus requiring higher doses or quantities), and may leave animals exposed to disease.

Requirements

Chapter 3.4 of the TAHC states that legislation should prohibit the sale of unlabelled, unregistered, substandard or falsified VMPs, and therefore only authorized products should be placed on the market. Legislation should implement the VMP classification system by stating the locations at which antimicrobials may be sold (as based on their classification) and should stipulate the ways in which the VMP distribution system should function. The locations at which antimicrobials may be sold include pharmacies and veterinary clinics, but also other establishments (such as feed distributors, supermarkets, pet shops or other retailers). Legislation may require the competent authority to issue a permit for any retailer or VMP provider that sells or distributes VMPs. Storage requirements may be imposed on VMP sellers, as well as rules relating to the proper disposal of unsold or expired stock. Any person that sells VMPs that require a prescription by a veterinary professional, is under an obligation to only sell antimicrobials upon the submission of such prescription (CXC 61-2005).

Zambia's *Medicines and Allied Substances (Agro-Veterinary Shops) Regulations (No 10 of 2016)* declares that a holder of a permit shall sell the veterinary medicines prescribed in the Second Schedule. The latter sets out the types of substances that may be sold at particular locations (Regulation 15). For example, the Agroveterinary Shop Class I includes those that may sell any prescription-only veterinary medicines, in addition to all pharmacy veterinary medicines and general sales veterinary medicines. This Class of shops may also include medicines imported with special authorization. The text also requires the competent authority to maintain a register of agroveterinary permits. Notably, in Regulation 13, the competent authority is tasked with considering the following factors when granting an agroveterinary permit: "(a) rural areas and districts where access to medicines is limited; and (b) peripheral areas of municipalities or cities, where access to medicines is limited."

All provisions on the obligations of sellers should be buttressed by clear sanctions that list and itemize behaviours that constitute offences (e.g. the sale of antimicrobials requiring prescriptions where the prescription has not been submitted to the seller). Zambia's *Medicines and Allied Substances (No 3 of 2013)* establishes offences for the manufacture, import, export, distribution or sale of "substandard, counterfeit, adulterated or misbranded" VMPs; expired VMPs; or VMPs advertised, labelled or packaged in a manner that is false or misleading (Sections 59–61).

In some countries, veterinarians are permitted to sell VMPs directly. Cabo Verde's *Law No. 30/VIII/2013 establishing veterinary safety norms, animal health and environmental safety for animal origin products*, allows the sale of VMPs that require prescription through pharmacists and veterinarians (in public or private service). For those that do not require prescription, in addition to the aforementioned classes, agricultural organizations/associations are permitted to sell or distribute VMPs to their members. The latter group is nonetheless prohibited from wholesale distribution. Burkina Faso's *Décret n°2018-0729 portant règlementation de la pharmacie vétérinaire* also prohibits VMP operators from selling directly to the public, with the exception of medicated feed to production associations (Article 41).

While there are clear advantages of direct sale by veterinarians in places where few pharmacies or retail outlets exist, the negative aspect is that this exposes veterinarians to potential influence by VMP manufacturers and may incentivize excessive use of antimicrobials. Therefore, mechanisms to prevent conflicts of interest

are important. The competent authority may be given specific powers to monitor and control prescriptions in such cases. In Norway, under the *Medicines Act*, only pharmacies can sell VMPs. Section 17 of the Act provides an exception which allows veterinarians to be authorized to sell VMPs by the responsible ministry when access to a pharmacy is difficult. In such cases, the VMPs must be sourced from a pharmacy.

Clinics, pharmacies, retailers and other establishments that sell VMPs may be required to keep records on the VMPs stocked and sold. The TAHC in Article 6.10.5 outlines the data to be kept, including: the product; date and quantity of supply; names of the prescriber and user; batch number and expiry date; and a copy of the prescription. The Codex CXC 61-2005 also lists the information requirements in records to be kept by distributors under Section 5.3. Canada has taken measures through the *Food and Drug Regulations (C.R.C., c. 870, as amended in 2020)* to better understand the amounts of antimicrobial VMPs sold in the country by requiring every manufacturer or importer who sells a veterinary drug in dosage form that contains an active pharmaceutical ingredient set out in List A of the Regulation, to submit an annual report identifying the total quantity sold for each drug and an estimate of the quantity sold for each intended animal species (C.01.612). List A contains antimicrobial active pharmaceutical ingredients and is published online and periodically updated, rather than included in the legislation (C.01.001(1)). Similarly in the United States, the *Animal Drug User Fee Amendments of 2008 amended the Section 512 of the Federal Food, Drug, and Cosmetic Act* requires the sponsor of a new animal drug to submit an annual report to the competent authority on the amount of each antimicrobial active ingredient in the drug that is sold or distributed for use in food-producing animals, including information on any distributor-labelled product.

The law may also establish a mandatory recall system to withdraw specific lots of VMPs from sale if found (or suspected) to be falsified, substandard or expired. This may also include VMPs withdrawn from sale in other countries due to safety or efficacy concerns. The recall system should include direct sales by veterinarians as well as wholesale and retail sales. Zambia's *Medicines and Allied Substances (No 3 of 2013)* calls upon the manufacturer, importer or person in possession of a recalled VMP to deal with or dispose of that VMP in such a manner as the competent authority directs (Section 46). Furthermore, the Act stipulates that no person should sell any VMP that is the subject of a recall notice.

Rules concerning storage practices may also be imposed on VMP sellers, including rules relating to the proper disposal of unsold or expired stock. Section 17 of the CXC 61-2005 and Chapter 6.10 of the TAHC stipulate that storage conditions should maintain the quality and concentration (stability) of the product up to the expiry date. Legislation may also reference the need to trace VMPs through their distribution, transport and sale (typically through labelling requirements) for the purposes of recall.

Electronic commerce (e-commerce)

Regulating sales of antimicrobials exclusively through traditional routes may result in higher and less appropriate uses of antimicrobials where there is the option to shift to self-diagnosing and online purchasing through internet pharmacies (Boyd *et al*., 2017). Online retailers may be less regulated (if at all). While e-commerce of pharmaceuticals, including VMPs, brings with it the benefits of price transparency and flexibility through 24/7 access, in particular in contexts where access to antimicrobials in rural and remote areas may be limited, e-commerce sales may nonetheless increase the risk of the sale of unregistered, substandard or falsified VMPs while also increasing the risk of AMR through self-diagnosis, misuse or excessive use of VMPs (Garcia *et al*., 2020). Because poorly- or non-regulated internet pharmacies can be part of criminal organizations, they also carry non-health-related risks such as consumer fraud, breach of privacy, stealing of personal data and possible hardware infections with malware and viruses (Macket and Nayyar, 2016). As such, the Global Action Plan recognizes the threats posed by the inadequate regulation of internet pharmacies and notes the associated poor enforcement at national level.

When the national legislation allows for the sale of VMPs online, laws should ensure that the requirements and safeguards for online sale are equally robust as for brick-and-mortar retailers or pharmacies. To ensure the legality of internet pharmacies, all such entities should have an approved logo and should be registered on a national website that lists the names. The *EU Regulation 2019/6* contains provisions regarding the online sale of VMPs. Online sales to natural or legal persons established in the European Union is allowed if the VMP is not subject to prescription. Member States may choose to also allow the online sale of VMPs for which prescriptions are required, if: (i) they can provide a secure system for their supply; (ii) sale is limited to persons established in their territory; and (iii) the supply shall only occur within their territory. Permitted internet pharmacies are also required to have the Commission-established logo, clearly showing the country where the site is located and a link to a national website listing retailers established in the Member State permitted to offer VMPs online (Article 104). The *Directive 2011/62/EU as regards the prevention of the entry into the legal supply chain of falsified medicinal products* targets online sales (which can be particularly vulnerable in the context of substandard and falsified medicine), by establishing an EU-wide logo to enable consumers to identify legitimate online pharmacies (Article 85).

Proposals regarding the regulation of online sales of antimicrobials range from a total ban (VE, 2013), to strengthened control measures for the online sales of antimicrobials with cybersecurity featuring prominently in regulatory controls (Garcia *et al.,* 2020). The requirements placed on the traditional retail of antimicrobials and VMPs would also apply to internet pharmacies. Critically, the sale of prescription VMPs would be contingent upon submission of a prescription issued by an authorized veterinarian. To facilitate this, countries may need to create a system of e-prescriptions and an accompanying online register to verify the veracity of such prescriptions. Penalties should be appropriately dissuasive, and enforcement rigorous (Garcia *et al.,* 2020).

As indicated in *EU Regulation 2019/6*, internet pharmacies may also facilitate cross-border sales of antimicrobial VMPs. Therefore, considering the difficulties in ensuring the appropriate and legal use of antimicrobials which may be subject to different requirements in different countries, the choice in the European Union has been to explicitly ban cross-border online sales of antimicrobial VMPs. In the absence of a complete cross-border ban in national legislation, regulators may consider imposing the same requirements as a domestic sale of the same VMP on permitted cross-border sales of antimicrobial VMPs. This may pose some difficulties in verifying prescriptions, which could require legal mechanisms to recognize foreign prescriptions as equivalent under given conditions. Additional challenges may be related to the official control of goods and being able to ensure the quality and legality of antimicrobial VMPs coming from abroad.

7.1.12. Use

Overview of key regulatory elements relating to the use of veterinary medicinal products

- Legislation may differentiate between veterinary medical uses and non-veterinary medical uses of antimicrobials, specifically by defining what is included under these two categories.
- Definitions of "treat" "control" and "prevent" may help to prevent a circumvention of any ban on antimicrobials for non-therapeutic purposes.
- Legislation may restrict or prohibit the use of antimicrobials for non-veterinary medical uses. In making this decision, regulators may wish to adopt a risk-based approach and must examine:
- the context in which such a restriction would operate;
- the antimicrobials or antimicrobial classes for restriction;
- whether alternatives are adequate and feasible (for example promoting biosecurity measures or changed production practices to prevent disease).

Overview of key regulatory elements relating to the use of veterinary medicinal products *(cont.)*

- The use of antimicrobials may be restricted to specific types of veterinary medical uses and legislation can stipulate which VMPs are used for a particular purpose.
- End users are to follow instructions on the label and as directed by the veterinarian.
- Where laws allow off-label or extra-label use, the specific conditions in which this is permitted should be circumscribed by law.
- Prudent and responsible use by animal producers should be encouraged through specific responsibilities (e.g. compliance with data-keeping, observance of withdrawal periods, refraining from using expired VMPs, and proper disposal).

Rationale

Three key issues arise with respect to the use of antimicrobials that are critical for promoting the responsible and prudent use of antimicrobials in the veterinary sector. The first issue, as the foregoing section outlines, is to ensure there are appropriate channels for access to antimicrobials that serve veterinary medical purposes (including treatment, prevention and control), and to ensure that end users follow the instructions on the label as well as those given by the prescribing or treating veterinary professional. The second issue, is that restrictions or prohibitions may be warranted relating to the use of antimicrobials for non-veterinary medical uses. Non-veterinary medical uses is defined in Article 6.9.2 of the TAHC as the "administration of antimicrobial agents to animals for any purpose *other than* to treat, control or prevent infectious disease; it includes growth promotion". The third issue, is setting up a favourable environment to support the responsible and prudent use by agricultural producers through appropriate biosecurity measures on farms and more broadly through robust plant health and animal health systems – this third issue is addressed in Section 9.1 of this Study.

As a preliminary observation, it should be recalled that VMPs can be restricted in use according to a national list of essential medicines and essential veterinary medicines (see Section 7.1.5 of this Study). These lists are different from the registry of authorized or registered products. Rather, these lists correspond to different levels of restrictions on use or the conditions for use. Furthermore, legislation may introduce restrictions related to group administration of antimicrobials for selected species or products.

Use of antimicrobials for growth promotion

The use of antimicrobials as growth promoters in the absence of risk analysis has been identified as a cause of AMR (FAO, 2021a), and national regulatory measures have been taken to restrict this practice since the 1980s. At the international level, FAO advocates the phasing out of the use of antimicrobials in animals for growth promotion in the absence of risk analysis (FAO, 2021a). The CXC 61-2005 (as amended in 2021) specifies that "responsible and prudent use of antimicrobial agents does not include the use for growth promotion of antimicrobial agents that are considered medically important" and that furthermore, "antimicrobial agents that are not considered medically important should not be used for growth promotion unless potential risks to human health have been evaluated through procedures consistent with the Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CXG 77-2011). The WHO recommends the complete restriction of all classes of medically important antimicrobials for growth promotion in food-producing animals (WHO, 2017b). Similarly, the WOAH holds that the responsible and prudent use of antimicrobial agents does not include their use for growth promotion in absence of risk analysis (OIE, 2020). The WOAH also stipulates that classes of the WHO category of Highest Priority Critically Important Antimicrobial Agents should be the highest priority for countries in phasing out the use of antimicrobial agents as growth promoters (OIE, 2020). Furthermore, the use of antimicrobials for growth promotion that belong to classes of antimicrobial

agents used in humans and animals should be terminated or phased out in the absence of risk analysis and off-label use of antimicrobial growth promoters should not be permitted. Finally, in its 2019 report to the Secretary-General of the United Nations, the Interagency Coordination Group on Antimicrobial Resistance calls on all Member States to phase out the use of antimicrobials for growth promotion, consistent with guidance from FAO, the WHO and the WOAH, starting with an immediate end to the use of antibiotics categorized as the Highest Priority Critically Important Antimicrobial Agents on the *WHO List of Critically Important Antimicrobials for Human Medicine* (IACG, 2019).

The WOAH data shows that out of 157 countries analysed in a survey, 69 percent did not use any antimicrobials for growth promotion. Ninety-six countries affirmed that they had enacted legislation restricting the use of antimicrobials for growth promotion, while 33 countries declared they did not use antimicrobials as growth promoters, even in the absence of a legal framework (WOAH, 2022). In the latter countries this was achieved through responses such as import controls and restricting registration (and labelling) to therapeutic uses only.

In 1986, Sweden was the first country to introduce legislation prohibiting the use of antimicrobial growth promoters. All antimicrobials for use in animals have since then been classified as veterinary medicines, with their use in animals becoming restricted to prescription only by veterinarians. In the European Union, *Regulation 1831/2003 on additives for use in animal nutrition* banned antibiotics as growth promoters from 1 January 2006, while *Regulation 2019/6* in Section 107(2) stipulates that "antimicrobial medicinal products shall not be used in animals for the purpose of promoting growth nor to increase yield." Thailand has also banned the use of all antimicrobials as growth promoters in food animals under *Notification of the Ministry of Agriculture and Cooperatives (2015)*. However, rather than opting for an outright ban, some countries have chosen to refer to risk analysis as the basis for decisions on whether to authorize or prohibit the use of antimicrobials for growth promotion.

All regulatory mechanisms designed to target antimicrobial use for growth promotion must be holistic and examine the range of impacts on different stakeholders. This includes understanding the rationale for using antimicrobials for non-therapeutic purposes in the first place. For example, farmers may use antimicrobials to boost productivity of their animals (by boosting their growth and preventing disease). Therefore, reducing the incidence of antimicrobials used for non-therapeutic purposes should be examined in tandem with other regulatory options and mechanisms, such as improving biosecurity conditions and improving production practices to facilitate healthy growth of animals and to prevent disease. The broader context of animal production should also be a consideration because farmers in many countries may not have the necessary financial capital to introduce these measures (ReAct, 2019).

Use of antimicrobials for therapeutic purposes

Separate to the use of antimicrobials as growth promoters, the nebulous concept of what is included in "treatment" or for "therapeutic purposes" may itself present challenges in the absence of clear definitions. For example, the use of VMPs in some countries can be authorized for "treatment", "control" or "prevention". The boundaries between "treatment" and "control" require definition in order to better differentiate the two types of use. The WHO guidance restricting medically important antimicrobials for routine use may then guide legislation to create lists of antimicrobials that could be used in prevention.

The terms prevention, control and treatment are defined by the TAHC in Chapter 6.9 as follows: "to 'treat' means to administer an antimicrobial agent to an individual or a group of animals showing clinical signs of an infectious disease"; "to 'control' means to administer an antimicrobial agent to a group of animals containing sick animals and healthy animals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of the disease"; and "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."

The CXC 61-2005 also has definitions for these concepts. Accordingly, "control" of disease/metaphylaxis is defined as: "Administration or application of antimicrobial agents to a group of plants/crops or animals containing sick and healthy individuals (presumed to be infected), to minimize or resolve clinical signs and to prevent further spread of the disease"; "prevention" of disease/prophylaxis is defined as: "Administration or application of antimicrobial agents to an individual or a group of plants/crops or animals at risk of acquiring a specific infection or in a specific situation where infectious disease is likely to occur if the antimicrobial agent is not administered or applied"; and "treatment" of disease is defined as: "Administration or application of antimicrobial agents to an individual or group of plants/crops or animals showing clinical signs of infectious disease."

The *EU Regulation 2019/6* differentiates between "metaphylaxis" and "prophylaxis". Methaphylaxis is defined as "the administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected" and prophylaxis as "the administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection." A veterinarian is required to provide justification for a veterinary prescription of an antimicrobial and indicate whether it is for metaphylaxis or for prophylaxis (Article 105). Furthermore, Article 107 states that antimicrobials can be used for prophylaxis only in exceptional situations, where the risk of infection or an infectious disease is very high, and the consequences are likely to be severe. Even in such cases, the use of antibiotic medicinal products for prophylaxis is restricted to an individual animal only. The Regulation prohibits the routine use of antimicrobials to compensate for poor hygiene, inadequate animal husbandry, lack of care, or to compensate for poor farm management. Antimicrobials reserved for the treatment of certain infections in humans cannot be used to prevent disease (Article 107).

Where legislation limits the use of antimicrobials for specific purposes, risk management may serve as a strategy to select the VMPs that are available for a particular purpose. Where use of antimicrobials is permitted for therapeutic purposes, some classes of VMP may permit administration to animals by authorized persons, including possibly the farmer. The Swedish *Regulations on Medicines and Drug Use (2023:103)* requires veterinarians to consider the various risks related to the product when selecting the type and dosage of the medicine, including the risks to the person administering the medicine, the risks to the animals, and importantly, the risk of contributing to the resistance to antimicrobials (Chapter 2, Section 1). The use of certain antibiotics is prohibited without a microbiological examination and assessment of resistance showing that there is no effective alternative (Chapter 2, section 11).

Beyond these concepts and more broadly, Section 6, Chapter 6.10 of the TAHC outlines key elements for responsible and prudent use of antimicrobials in veterinary medicine. The Chapter sets out the responsibilities of competent authorities as well as those of a range of stakeholders such as VMP manufacturers and distributors, food producers, and veterinarians. The responsibilities of the competent authority are addressed in detail throughout this Study. Detailed provisions on responsibilities of veterinarians are provided in Article 6.10.6 including: factors to guide the choice of antimicrobials; factors to guide appropriate use and treatment protocols; the data required for record-keeping; and labelling instructions for products distributed as VMPs. The Article also requires that training and continuous professional development are maintained in the use of antimicrobials.

Off-label or extra-label use

Off-label or extra-label use of VMPs pertains to the use of the product in a manner different from that indicated on its label. Extra-label uses include: (i) varying the dosage (and dosage forms); (ii) changing the frequency of administration; (iii) using the product to treat a different disease, animal species or age of

animal than what is indicated; and (iv) changing the manner of administration (Manitoba, undated). The risk inherent in this practice is that the product may have reduced or uncertain efficacy for the conditions being treated, create higher risks for AMR in the future, and the residues may be higher than when applied in accordance with label instructions.

Legislation may nonetheless allow off-label or extra-label use, and if so, must circumscribe the situations in which this is permitted, and the rules to be followed. Such conditions typically relate to the status of the animal, for example, when the animal is in severe pain or in a life-threatening condition or where no other VMP is available to treat the condition. Veterinarians in some countries are permitted to issue prescriptions for extra-label use and thereby assume responsibility. Extra-label uses may also be permitted for other categories of professionals, or even livestock or aquaculture producers.

The CXC 61-2005 states that, for food producing animals, the off-label use of a veterinary antimicrobial agent may be permitted in appropriate circumstances and should comply with national legislation, including through the use of approved or appropriate withdrawal periods. According to this Code of Practice, it is the veterinarian's responsibility to define the conditions of use including the dosage regimen, the route of administration, and the duration of the administration and the withdrawal period. In addition, it states that human health risks related to foodborne AMR must be an important factor when considering the off-label use of VMPs in food producing animals. The TAHC states that the use of compounded VMPs containing antimicrobial agents, and the extra-label or off-label use of registered VMPs containing antimicrobial agents should be limited to circumstances where an appropriate registered product is not available (Article 6.10.6.3 of Chapter 6.10). In the United States, the *Animal Medicinal Drug Use Clarification Act of 1994* and the *Federal Regulation Code 21 CFR 530* allows for the extra-label use of drugs by veterinarians under certain conditions. Such use must occur in the context of a valid veterinarian–client–patient relationship and cannot be administered through feed nor result in any residue that presents a risk to public health (21 CFR 530.10-11). Stricter requirements for extra-label rules are established for food-producing animals. Veterinarians are required to keep extensive records on the extra-label use (21 CFR 530.5).

Responsible and prudent use

Under Article 6.10.3 of the TAHC, VMPs containing antimicrobials should only be used by a veterinary professional. Veterinarians are required to follow evidence-based clinical guidance on the proper use of antimicrobials for animal production. Reporting is often obligatory in terms of types and amounts of antimicrobials prescribed or administered, as well as any pharmacovigilance-related data (for example, on adverse effects).

Legislation should set out the responsibilities of livestock and aquaculture producers. Chapter 6.10 of the TAHC sets out responsibilities for owners of food producing animals. In addition, these responsibilities often extend towards limiting environmental dimensions of AMR. The *EU Resolution 2019/2816(RSP)of 2020* indicates that the largest source of pharmaceuticals (of all types, and among them antimicrobials) that enter the environment, is a result of use and disposal. Livestock and aquaculture producers may be tasked with responsibilities across various types of agriculture laws, relating to: the responsible and prudent use of antimicrobials; the implementation of health and welfare programmes; compliance with the withdrawal periods of VMPs to ensure residue levels in foods of animal origin do not present a risk to the consumer; refraining from using expired VMPs; and disposing of all unused VMPs and waste material in accordance with the label. Ethiopia's *Veterinary Drug and Feed Administration and Control Proclamation (No. 728 of 2011)* requires disposal to be carried out in accordance with the directions of the competent authority. Ghana has specific regulatory requirements for aquaculture producers under its *Fisheries Regulations (2010) L.I. 1968,* which requires the prescription of a veterinary officer for the use of drugs in aquaculture (Section 64). Sections 75–78 establish rules on the positioning of pens and cages, requiring that these do not hamper

water quality among other aspects. Agricultural extension services may be tasked with monitoring producers' use of antimicrobials, advising on the observance of withdrawal times, and offering guidance on how to correctly dispose of waste from antimicrobials and from animals treated with antimicrobials. Producers may be required to cooperate with authorities in gathering data on antimicrobial use, and specifically to permit the taking of samples for this purpose. In order to prevent the dispersal of antimicrobials into the environment, producers may be required either to return unused or expired antimicrobials to the sales or distribution point or may be required to follow specific instructions for the safe and proper disposal of antimicrobials. In Sri Lanka, under the *Aquaculture Management (Disease Control) Regulations (2000)*, inspectors are required to supervise the use of antibiotics in fish feed and a mandatory waiting period is required before fish treated with antibiotics can be harvested and placed on the market for human consumption (Section 13). In Norway, under the *Regulations on measures against diseases and zoonotic agents in animals (Animal Health Regulations)*, livestock owners must ensure that an up-to-date journal is kept with necessary individual and collective health information on the animals, which includes any actions taken in the treatment of diseases and injuries of the animals (Section 9).

For a more detailed analysis on the obligations on livestock and aquaculture producers, see Section 9.1 of this Study.

7.1.13. General requirements relating to veterinary medicinal product operators

Overview of key regulatory elements relating to veterinary medicinal product operators

- Legislation requiring the licensing of veterinary medicinal product (VMP) operators may impose terms and conditions established in connection with the licence that are often enumerated in legislation:
  - record-keeping and reporting;
  - compliance with inspections;
  - complying with measures to ensure the quality of VMPs, including self-auditing, recall plans, compliance with storage rules, etc.
- All VMP operators have the duty to cooperate with the competent authority during inspections of their premises and should facilitate access to all areas.

Rationale

With a view to facilitating regulatory control, licences offer a mechanism to control activities along the VMP lifecycle, including through specific responsibilities for persons holding such licences. This enables authorities to control of the types and quality of antimicrobials on the market, as well as the production and distribution processes. A licensing system is complemented by an inspections and enforcement system.

Licences

Legislation should require the licensing of all VMP operators, including those manufacturing, importing, selling or otherwise distributing VMPs (as well as for any biologicals and certain other types of ingredients and substances for use in VMPs). Legislation may stipulate: (i) specific criteria for the authorization of the activity, such as structural requirements relating to the premises; (ii) procedural requirements relating to manufacturing, hygiene or other processes; and (iii) compliance relating to enumerated conditions of

the licence. Burkina Faso's *Décret n°2018-0729 portant règlementation de la pharmacie vétérinaire* requires authorization of the veterinary authority (in addition to other authorities responsible for regulating commercial activities), and authorization is subject to inspections (Articles 19 and 20). This Decree sets out a range of other responsibilities of VMP operators, including: (i) self-monitoring of operations; (ii) complying with storage and transport requirements; (iii) having appropriate locations and adequately trained staff; (iv) complying with specific obligations relating to maintaining quality standards, including ensuring each lot is subject to quality control before distribution; (v) providing information relating to any risks to public health raised in connection with their products; and (vi) establishing an emergency recall plan (Articles 44–49).

Licensing may be regulated through VMP legislation, while licensing of agricultural producers may be regulated in general legislation on agriculture, aquaculture or animal health and production. In some jurisdictions, certain licensing requirements may be imposed through general commercial legislation or business licensing laws, or even in specific licensing laws.

Inspections

Depending on the jurisdiction, legislation may set out various categories of inspections.

i. Routine vs for-cause inspections: Routine inspections are based on inspection plans underpinned by a risk-based approach that guides prioritization. For-cause inspections are undertaken in response to specific triggers such as a report or related incident.

ii. Announced vs unannounced inspections: Announced inspections enable the operator to prepare for the regulatory visit, make all relevant personnel available and ensure that all documentation is retrieved and assembled for inspection. Unannounced inspections enable regulators to determine whether the operator is always in compliance with required rules. However, these inspections should have a reasonable justification as they are a less effective use of time for both the inspector and the operator.

iii. Re-inspections: One or more follow-up inspections may be necessary where serious or multiple non-compliant issues were identified in the initial inspection.

iv. Desktop/paper inspections: Desktop/paper inspections are in-person or remote inspections of records and other documentation gathered on site or through a request for specific documentation.

Legislation should identify the body of inspectors in charge of enforcing legislation and designate the authority under which the inspectors operate. Coordination is necessary where there is more than one body of inspectors with competence for inspecting VMPs.

Legislation should also include a provision on the designation of official laboratories to test VMPs for quality and efficacy in order to identify substandard or falsified VMPs. Depending on the country's circumstances and resources, an official laboratory may be public or private and may be located within or outside the country.

All VMP operators have the duty to cooperate with the competent authority during inspections of their premises and should facilitate access to all areas used for sale, storage and manufacturing, in addition to their records. With regard to general enforcement, in Botswana, under the *Medicines and Related Substances Act* (2018), VMP operators must allow inspectors entry to all premises where medicines or medicated feeds are stored, used, handled, dispensed, manufactured or sold, with or without prior arrangement. The inspector is to be given unhindered access to such premises with the right to take samples of any medicines on the premises and to carry out investigations (Section 47). Burkina Faso's *Décret n°2018-0729 portant règlementation de la pharmacie vétérinaire* imposes periodic inspections on VMP operators, including at

places of manufacture and import, and grants the specific power to request and examine all records relating to operations (Article 70). A report, to be shared with the VMP operator, is to be completed as part of the inspection process. Samples are to be collected by inspectors and sent to VMP quality control laboratories established under the Economic Community of West African States (ECOWAS) *Regulation No 4/2006* (Article 73). Rwanda's *Arrêté ministériel n⁰008/11.30 du 18/11/2010 portant organisation de l'exercice de la pharmacie vétérinaire* allows inspectors to seize products that may create a risk to human health, in addition to sealing containers that are suspected of containing non-compliant VMPs (Articles 28 and 29). Evidence of offences shall be recorded in inspection records (Article 27). It is prohibited to hinder the work of an inspector (Article 26).

Duty to keep records and cooperate during inspections

Legislation should require the VMP operator to keep records on the quantity and types of antimicrobials in their possession, the numbers that are sold or distributed, the quantity disposed of and the manner of disposal. Article 6.10.5 of the TAHC sets out the types of data that should be stored by VMP distributors and retailers including: identification of the product; date and quantity of supply; the names of the prescriber and user; batch number and expiry date; and a copy of the prescription. The CXC 61-2005 contains specific recommendations for livestock and aquaculture producers in keeping records; these include: (i) the name of the veterinary antimicrobial drug/active substance and batch number; (ii) the name of supplier; (iii) date of administration; (iv) identification of the animal or group of animals to which the veterinary antimicrobial drug was administered; (v) the clinical conditions treated; (vi) the quantity and duration of the antimicrobial agent administered; (vii) withdrawal periods; (viii) result of any laboratory tests; (ix) results of treatment carried out; and (x) the name of the prescribing veterinary professional. Legislation may also include a duty to report incidents of negative effects that are brought to the attention of licensees (particularly manufacturers and sellers).

The United Kingdom's *Veterinary Medicines Regulations (2013)* has extensive record-keeping requirements. Veterinary surgeons, when administering VMPs to food-producing animals, are required to enter specific information on the animal keeper's records or provide the same information in writing to the keeper (Regulation 18). This information includes: (a) the name of the veterinary surgeon; (b) the name of the product and the batch number; (c) the date of administration of the product; (d) the amount of product administered; (e) the identification of the animals treated; and (f) the withdrawal period. The keeper of food-producing animals also has varying record-keeping requirements at the point of acquisition, administration and disposal of VMPs (Regulation 19). These records are to be kept for at least five years (Regulation 20).

7.1.14. Post-marketing surveillance

Overview of key regulatory elements relating to post-marketing surveillance

- Antimicrobial use surveillance systems should:
  - be based on a One Health approach;
  - be based on the country's context;
  - collect data from three strategic sources: pharmaceutical manufacturers, points of sale or distribution, and from the end user.
- The legal framework should set out clear rules relating to data sharing and consider data privacy rights and norms.

Rationale

Monitoring and surveillance systems are critical to address AMR challenges and have been highlighted as such in international reference standards. Antimicrobial use as well as AMR monitoring and surveillance programmes help limit the proliferation of resistant microorganisms and the emergence of new strains. Owing to the complexity of AMR prevention, the information sourced from inspections should be compiled alongside data reported by VMP operators. This generates a comprehensive view of how antimicrobials are produced, distributed and used, to inform policy-making and regulatory action. The early detection of AMR could lead to the restriction or deauthorization of a VMP or could incentivize the development of more effective or non-resistant alternatives.

Requirements

The TAHC provides rules for the harmonization of national AMR surveillance and monitoring programmes, and Article 6.10.3 sets out details related to post-marketing antimicrobial surveillance. The CXC 61-2005 stipulates 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. To fully capture the phenomena of AMR, this information should be gathered using a One Health perspective, and to the extent possible, cover both animals and humans to provide a more complete picture (O'Neill, 2016). As per the scope of this publication, only surveillance in the agriculture sector is considered.

Legislative frameworks should establish effective antimicrobial use surveillance systems that collect data from three strategic sources: pharmaceutical manufacturers, points of sale or distribution, and from the end user (FAO and WHO, 2019). Thus, surveillance is related to the national inspection regime in that the same subjects and actors are involved, but surveillance and inspections programmes are often conducted in parallel. However, surveillance is designed to detect adverse effects from antimicrobial use – such as AMR – rather than controlling compliance.

Surveillance at manufacturer-level involves mandating pharmaceutical companies to disclose information annually about the quantity of antimicrobials placed on to the market and their stated purposes and applications. The data gathered should include in which sector (human, animal, crop) the product is purchased, the class of antimicrobial, and whether it was for domestic or foreign markets (FAO and WHO, 2019). Point of sale data covers importers, wholesalers and retailers. Surveillance also includes a review of the record-keeping obligations of pharmacists and veterinary paraprofessionals. Sweden's *Regulation on the authorities' obligations to disclose information on medicines for animals (2023)* obliges the monitoring authority upon a request from the National Veterinary Institute, to provide information on prescribed and dispensed antimicrobials for animals. The information must contain the identity of the animal owner and the person who prescribed the drug (Section 3). Under Section 4, the National Board of Agriculture is required to provide similar information to the National Veterinary Institute. With this information, fulfilling its role under the *Regulation Instructions for the National Veterinary Institute (2023:99)*, the National Veterinary Institute can undertake its role in monitoring and analysing AMR resistance in animals and in food, and also promote the rational use of antibiotics for animals (Section 2). To facilitate a One Health approach, a similar task is given to the Public Health Authority under *Regulation (2013: 1020*). The Public Health Authority is mandated to ensure the prudent and appropriate use of antimicrobials in humans and animals by gathering and analysing information, and actively imparting knowledge on issues related to AMR.

The legal framework should also set out clear rules relating to data sharing and consider data privacy rights and norms. Timely communication between relevant authorities, particularly if they reside in different ministries, may at times be compromised over uncertainties of which data can be shared without risking the

privacy of the data sources. Legislative provisions regarding data sharing may be found in VMP legislation but would more likely be addressed in other national laws on data privacy and the rules regarding the use of personal data by government.

Finally, it is important that countries set up surveillance programmes that take into account their specific challenges. According to a WOAH survey conducted in 155 countries in 2017, 3 countries observed that owing to the flooding of illegal VMPs on the market, it was difficult to determine the specific antimicrobials that were actually used in animals (OIE, 2018a). This confusion may be compounded where borders are porous; thus regulatory control and data management of imports is problematic. Where the market is too small for bulk purchases, human medicines may end up being used for animals, or veterinarians may import small quantities for use exclusively on livestock (OIE, 2018a). In such cases, surveillance programmes may prioritize other data sources, such as from extension services as well as livestock and aquaculture producers themselves. Data on antimicrobial use at farm-level is necessary to understand the actual practices regarding their use.

Post-marketing surveillance in the form of both general epidemiological surveillance and specific surveillance on the impact of specific antimicrobial agents is also necessary. General epidemiological surveillance systems can be expanded to include microorganisms resistant to antimicrobial agents, while specific surveillance should evaluate resistance in target animal pathogenic agents, as well as food-borne pathogenic agents, and commensals if relevant and possible. According to Article 6.10.3 of the TAHC, data from pharmacovigilance programmes, including lack of efficacy of VMPs, should inform the AMR strategy.

7.1.15. Pharmacovigilance

Overview of key regulatory elements relating to pharmacovigilance

- Pharmacovigilance programmes should be established that record and report adverse effects of VMPs.
- Periodic Safety Update Reports (are often a required registration condition imposed on VMP operators such as manufacturers and are required to be submitted to the competent authority at set intervals.

Rationale

Pharmacovigilance consists of the collection of data on adverse effects of pharmaceuticals, and the detection, assessment, monitoring and prevention of those effects. While the purpose of VMP regulatory controls is to ensure safety and efficacy, it may not be possible to ascertain the full impact or effects of a VMP until it is in use. Risks and problems may arise once a VMP is on the market even where all VMP operators have fulfilled their regulatory obligations. Pharmacovigilance enables regulatory action to protect human and animal health and may result in product improvement as well. For instance, a newly discovered adverse effect might lead to the addition of a warning notice on the product label, whereas manufacturing problems might result in an order to make improvements to manufacturing processes.

Requirements

According to the TAHC, the AAHC, and the CXC 61-2005, regulatory authorities should establish pharmacovigilance programmes for the monitoring and reporting of adverse reactions to VMPs, including where efficacy is found to be lower than expected (possibly caused by AMR), and this may aid in re-evaluating the authorization of the VMP. Pharmacovigilance focuses on the effects of VMP use *even when all regulatory requirements are fulfilled* throughout the lifecycle.

Quality control through pharmacovigilance is enabled by data from VMP manufacturers or operators in the form of Periodic Safety Update Reports or Periodic Summary Updates, as part of registration requirements. The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) has provided guidance on setting up legal frameworks for pharmacovigilance. The VICH views the harmonization of pharmacovigilance legislation as a way to save resources, facilitate the sharing, exchanging and pooling of data, and improving pharmacovigilance overall (VICH, 2018). The VICH *Guideline 24 on Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports* provides guidance on setting the scope for pharmacovigilance legislation, internationally harmonized definitions for key terms, as well as setting up the basic process for adverse event reporting (VICH, 2007). The VICH *Guideline 29 on Pharmacovigilance of Veterinary Medicinal Products: Management of Periodic Summary Update Reports* gives direction on how to standardize data for a Periodic Summary Update that contributes to a harmonized approach for the detection and investigation of adverse events for VMPs. The Periodic Summary Updates are submitted to the competent authority at set intervals to support the continued marketing and the adequacy of the approved labelling of the VMP; it should include an analysis of all adverse event reports received during the reporting period (VICH, 2006).

Norway, under the *Medicines Regulation (2009)*, mandates pharmacovigilance on each holder of a marketing authorization. It states that a person in possession of such authorization shall have at their disposal a sufficiently qualified person who is responsible for pharmacovigilance. This person's responsibilities include: (i) creating and managing a system to ensure that information on suspected adverse reactions reported to the company's employees and other representatives are collected and evaluated and made available to the relevant authorities; (ii) preparing reports as required by the competent authorities; (iii) ensuring that any requested disclosure regarding the risk-benefit ratio of a VMP is promptly and fully answered (Section 10a-2). Furthermore, the holder of a marketing authorization shall record all suspected serious adverse reactions and suspected unintended effects in humans and animals (Section 10a-3). Similarly, in Australia, pharmacovigilance is a legal obligation for those who have registered or listed a medicine under the *Therapeutic Goods Act (1989)* subsection 28(5)(e) and the Regulation 15A of the *Therapeutic Goods Regulations (1990)*. These persons are required to comply with record-keeping requirements and the reporting requirements set out in the document published by the Therapeutic Goods Administration titled *Pharmacovigiliance Responsibilities of Medicine Sponsors*. The publication, among others, requires the holder of the registration to report any cases of life-threatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of bacterium.

In Mali, as per the *Law No 2016-004 governing the veterinary pharmacy*, veterinary doctors and other health professionals are required to report to the competent authority any undesirable effects occuring on humans or animals likely to be attributed to a veterinary drug (Article 29). Under *EU Regulation 2019/6*, those holding marketing authorizations for antimicrobial VMPs may, when such authorization is issued, be required to conduct post-authorization studies in order to ensure that the benefit-risk balance remains positive given the potential development of AMR (Article 36). Further requirements are placed on the Member States themselves to collect comparable data on the volume of sales and on the use of antimicrobials used in animals, to enable the evaluation of the use of such products in food-producing animals at farm level (Article 57).

7.2. Feed management

Relevance of feed management

The regulation of feed ingredients and feed additives (including those with antimicrobial properties or those used as alternatives to antimicrobials), as well as medicated feed are all important in controlling what antimicrobials enter the feed chain for (terrestrial and aquatic) animals and the food chain for humans

(via food-producing animals). Indeed, food safety control systems include ensuring the safety of feed entering the food chain (see Section 8.1 of this Study for more on food safety). Some additives which are not antimicrobials may nonetheless have antimicrobial properties and may result in the development of AMR. This might be the case for some additives used for bacteria control in the production chain or used as feed ingredients (such as copper or zinc). Furthermore, the residues of these types of feed additives or ingredients in the manure of animals that have ingested the substances may result in the contamination of soil and water. As these substances and ingredients may create pathways for AMR (FAO, 2020c), it follows that an identification of the regulatory mechanism for the authorization, restriction or prohibition of specific additives in feed production would be relevant for AMR.

Where is feed regulated?

Animal feed legislation refers to the body of laws that covers the authorization, composition, production, distribution, import and export, sale and use of feed. These aspects may be regulated in stand-alone feed legislation, in food safety legislation, in general veterinary (animal health or production) legislation, VMP legislation, in agriculture inputs or agriculture legislation, as well as in fisheries or aquaculture legislation. Animal feed legislation may differentiate among the types of feed according to their purpose/use.

7.2.1. General elements of feed management

Overview of key regulatory elements of animal feed management relevant for addressing antimicrobial resistance

- Legislation should clarify whether certain feed ingredients or additives are considered as veterinary medicinal products (VMPs) or medicated feed by having clear definitions of feed, feed ingredient, feed additive, and medicated feed.
- Legislation should identify the competent authority responsible for all stages of the feed lifecycle; where more than one authority is involved, mechanisms for coordination are necessary.
- The competent authority may prohibit or restrict, at any time, the use of:
  - a feed product, ingredient or additive with which a health risk has been identified;
  - production practices.
- All feed that is distributed should be registered/authorized.
- Feed operators are ultimately responsible for the feed within their operations and put on the market; licensing and inspection schemes may be used by the competent authority to monitor these operations.
- Legislation should set up a traceability system, as well as provisions for recall or withdrawal; for these purposes, feed operators are required to keep records one-step-forward and one-step-back.
- In order to incentivize the use of certain feed additives or substances that promote health (thereby reducing the need for antimicrobials), the competent authority may:
  - permit the use of certain health claims or labelling information in the prescribed manner;
  - fast-track registration procedures.

Key functions of the competent authority

All aspects of the feed lifecycle should be regulated. These include the establishment of feed standards (and inspection/enforcement); registration of feed, feed additives and feed ingredients; feed production/manufacture; labelling and packaging; and advertising. Both the *Codex Alimentarius* and the WOAH have addressed different elements of the feed lifecycle in international reference standards. Legislation should identify the competent authority for all these stages, and these may include the veterinary or agriculture authority, aquaculture authority and even possibly local authorities (the latter are usually involved in inspections and enforcement). National Codex Committees or the competent authority for feed may have the mandate to develop, approve and/or implement feed standards. Where there is more than one agency responsible for feed management, coordination among them is essential. Coordination is also important between the authority responsible for feed and those responsible for VMPs, food safety, as well as animal health and production. In the Bahamas, *the Animal Health and Production Act (No. 7 of 2016)* establishes the position of the Director of Veterinary Services, who shall be responsible for administering and carrying out the objectives of the Act (Article 5). The Director's functions include the regulation of all matters related to animal health and production (Article 6(2)) and specifically set standards, import requirements and labelling requirements for feed as part of their overall responsibility to regulate the use of animal feed (Article 39).

Feed standards may address quality, safety, labelling and packaging as well as nutritional composition requirements. They may be used to prohibit or restrict the use of certain ingredients or certain production/processing practices. Ethiopia, under *the Veterinary Drug and Feed Administration and Control Proclamation No. 728/2011*, requires that no feed or feed additive may be used unless it complies with the quality standards issued or adopted by the competent authority (Section 14).

Legislation should empower the competent authority to prohibit or restrict, at any time, the use of a feed product, ingredient or additive with which a health risk has been identified. Such a mandate enables the inclusion of (different types of) antimicrobials in the categories of what is prohibited or what is restricted. Norway, in its *Regulation on additives for use in animal feed (2005)*, has placed limits on the use of copper in feed for piglets. The Codex *Guidelines on the Application of Risk Assessment for Feed (CAC/GL 80-2013)* may guide the risk analysis process undertaken by the competent authority to: (i) set maximum limits for undesirable substances, such as contaminants and residues; and (ii) may control the use of certain substances (such as antimicrobials) and production processes.

Authorization/Registration of feed, feed ingredients and feed additives

Where systems are already in place for the authorization or registration of feed, feed ingredients and additives, legislation typically prohibits the importation, production, sale, distribution or use of unregistered feed, feed ingredients or feed additives. Exceptions to registration requirements should be specified in legislation, which often includes: for research, laboratory analysis, for emergency situations, or for feed that accompanies animals imported specifically to participate in fairs, exhibitions or events. Authorization/registration might be subject to certain conditions or be limited to certain uses and legislation should clearly set out these procedures for authorization. For example, the authorization process may include detailed registration or the development of lists of authorized (or prohibited) feed, feed ingredients and feed additives. In addition to these lists, some countries include restrictions on the use of certain ingredients or additives, e.g. on the use or mixing of additives.

While there is variation in the different types of antimicrobials that may be added to feed, including antibiotics, antivirals or coccidiostats dewormers, there may be varying interpretation among countries (and international organizations) in how these antimicrobial substances are regulated. As previously mentioned in Section 1.1, the WOAH definition of antimicrobial agents specifically excludes "anthelmintics and substances

classed as disinfectants or antiseptics" (WOAH, 2022). In the European Union, rules on additives for use in animal nutrition are established in *Regulation 1831/2003* which allows coccidiostats and histomonostats to be used as feed additives. As a starting point it is useful to define "medicated feed" and "feed additives" in national legislation, with special attention to antiparasitics. The Codex *Code of Practice on Good Animal Feeding (CXC 54-2004)* defines "medicated feed" as any feed which contains veterinary drugs as defined in the Codex Alimentarius Commission's *Procedural Manual* (FAO and WHO, 2023b).

Certain ingredients or additives (for e.g. enzymes, probiotics, prebiotics, essential oils or yeasts) that may have beneficial effects on animals (and thus reduce the need to use antimicrobials) may be incentivized in legislation through rapid/fast-tracked registration.

Licensing of operators and associated responsibilities

Feed operators are ultimately responsible for the feed within their operations and that are put on the market. Legislation may establish licensing requirements for certain types of feed operators: feed producers and feed mills, packaging, sale, import and export, etc. In Malaysia, under the *Feed Act (2009)* the importing of feed and feed additives is conditional on licensing by the Feed Board (Article 9). Such a licence will be valid until the end of the calendar year in which it commences (Article 10) and can be renewed upon application (Section 12). Different requirements may be established depending on the activity. The licensing scheme may be monitored by the competent authority through inspections.

In addition to complying with safety and quality standards, feed operators are required to take all measures necessary to prevent contamination of feed and source the ingredients and additives only from licensed operators. Feed operators may be required to follow good manufacturing practices, undertake self-assessment (as per the CXC 54-2004), and where applicable, follow Hazard Analysis and Critical Control Point (HACCP) principles, to secure compliance with relevant standards. Furthermore, specific rules may appear in legislation regarding feed safety and quality. Feed, feed ingredients and feed additives should not be produced, processed, stored, transported or distributed in livestock facilities or aquaculture establishments (or using equipment) where incompatible operations may affect their safety (CXC 54-2004). Key hygiene and risk prevention principles are applicable at all these stages. In Armenia, *Law No. HO-141-N "On animal feed" (2014)*, requires feed and feed additive producers to introduce HACCP systems to provide for feed safety. The competent authority is tasked with supporting these producers in introducing the HACCP system (Article 7).

The Codex *General Principles of Food Hygiene (CXC 1-1969)* calls for food producers to implement control measures to prevent the contamination of feed. Legislation may introduce: (i) specific hygiene rules to prevent feed contamination by pests, or by chemical or biological contaminants, including antimicrobials and antimicrobial-resistant microorganisms; (ii) good agricultural and manufacturing practices; and (iii) risk analysis principles.

Traceability of feed, ingredients and additives is also important for ensuring safe feed. Legislation should underpin the traceability system for feed, feed ingredients and feed additives; this system is linked to the duty of operators to keep records –one-step-forward and one-step-back (CXC 54-2004). In Seychelles, where feed and food are both regulated under the *Food Act (No. 8 of 2014),* any person placing food or feed on the market must ensure adequate labelling or identification to facilitate their traceability. Every food and feed business operator is further required to ensure that all raw materials and other substances used and incorporated in food and feed at all stages of production, processing and distribution, shall be traceable to the source of purchase (Article 14).

Where withdrawal or recall is required feed operators should take action, e.g. in the case of non-compliance with safety or quality standards. Also, operators should be required by law to inform the competent authority where a feed, feed ingredient or feed additive does not meet safety standards (CXC 54-2004). The legislation should include a system for detection and rapid response for products that create a hazard to human or animal health that have been placed on the market. Legislation may require the development of contingency plans in response to emergencies involving feed and feed ingredients. In the Gambia, these topics are regulated under the *Food Safety and Quality Act (2011)*. This Act requires both food and feed business operators to immediately initiate procedures to prevent the products that do not meet safety requirements from reaching the (distribution) market (Article 38). If the product has left the operators' control, the latter are required to withdraw the product from the market and inform the competent authority (Article 38).

Labelling and packaging

Labelling is particularly important for medicated feed or feed containing additives that have antimicrobial effects. Feed legislation should set out specifications on the minimum information that should appear on the label. Legislation may stipulate the manner in which the information is presented, particularly for products that may be sold in bulk or sold online. This may include the use of pictograms. In Malawi, the power to establish labelling requirements is created under Section 3 of the *Fertilisers, Farm Feeds and Remedies Act (No. 12 of 1970)*, which stipulates that no person shall sell any feed unless the container in which it is sold complies with the prescribed requirements and is branded, labelled, marked or sealed in the prescribed manner. The CXC 54-2004 provides guidance on minimum labelling requirements, which include, *inter alia*: the species or category of animals for which the feed is intended; the purpose for which the feed is intended; and the feed ingredients, including additives, in descending order of proportion. The need for a prescription may be indicated on the label for medicated feed.

Legislation may also restrict the claims on the label of certain properties or special uses that cannot be verified (or that are not easily verifiable), such as, that it cures or prevents a disease. In considering such restrictions, a balance must be struck between allowing claims relating to certain substances that could have beneficial health impacts and reduce the need for antimicrobials. These include in-feed enzymes, competitive exclusion products, acidifiers, plant extracts, nutraceuticals, essential oils, yeast, prebiotics and probiotics. One method by which these feed additives may be promoted is to legally permit claims related to "health" or "growth" for these substances where they are proven effective. Different legal mechanisms can help governments to introduce feed quality and nutrition requirements. These include establishing minimum nutritional requirements for feed products to be registered, and regulating the use of health claims in labelling information for certain feed ingredients and substances. In jurisdictions where health claims are prohibited in legislation for feed additives, the consumer is not able to recognize the benefits of these additives, and thus there may be less motivation for the industry to spend considerable resources in developing and producing them.

7.2.2. Medicated feed

Overview of key regulatory elements for medicated feed

- Legislation should include a definition of "medicated" feed.
- Legislation should state that medicated feed is subject to the same rules as veterinary medicinal products (VMPs) for authorization, production, labelling, use, prescription, sale and use. Different methods of stating this include:
  - defining "veterinary medicinal product" to include medicated feed where this is feasible in the legal framework;
  - incorporate direct reference to VMP legislation in feed legislation, where feasible;

Overview of key regulatory elements for medicated feed *(cont.)*

- establishing clearly the authority responsible for medicated feed, feed and VMPs and where required ensure frameworks for coordination.

- Feed mills and other establishments that produce and sell medicated feed may have special authorization or operation requirements that align the regulatory regime for these products with that of VMPs.

Medicated feed, which is feed that contains VMPs (including antimicrobials) has veterinary medical uses and non-veterinary medical uses. Medicated feed is used commonly in intensive production systems to prevent the spread of disease. This type of feed is frequently produced and sold under the same regulatory framework as regular feed, and therefore legislation should ensure that medicated feed complies with the requirements of other VMPs. In Canada (British Colombia), the *Veterinary Drugs Act ([RSBC 2018)* holds that no person can manufacture or sell medicated feed or veterinary drugs, unless they have a valid licence to do so and they are either a pharmacist or a veterinarian (Section 3 of Chapter 2). Section 4 regulates the licensing of both VMPs and medicated feed and establishes requirements for both.

Any applicable rules, prohibitions and restrictions on VMPs would apply to medicated feed. In laws where medicated feed is not included in the definition of a VMP, such laws may include explicit provisions of VMP legislation that apply to certain aspects of medicated feed operations (e.g. registration, licensing of operators, surveillance, etc). The feed law may also be amended to state that requirements under the country's VMP laws should apply to medicated feed operators. The law should identify the responsible authority for medicated feed, given that it is possible that different authorities may be responsible for regulation of feed and regulation of VMPs. In the latter case, coordination is necessary.

Legislation should define medicated feed in order to delineate a specific sphere of regulation as to which rules apply to what products. The Codex *Procedural Manual* defines this term as "any feed which contains veterinary drugs" (FAO and WHO, 2023b). Another example of a definition comes from Canada, where under the *Feeds Regulations, 1983 (SOR/83-593)* where this term means "a mixed feed that contains a medicating ingredient", while the same Regulations define a "medicating ingredient" as "(a) a substance that is intended for use in the prevention or treatment of disease in livestock or (b) a substance, other than a feed, that is intended to affect the structure or any function of the body of the livestock, and that has assigned to it a drug identification number pursuant to the Food and Drugs Act" (Section 2(1)). The European Union defines "medicated feed" in *Regulation 2019/4* as "feed, which is ready to be directly fed to animals without further processing, consisting of a homogenous mixture of one or more veterinary medicinal products or intermediate products with feed materials or compound feed" (Article 2(a)).

The law may require that where a VMP has been added to feed, such medicated feed should be *registered* as a VMP in order to facilitate consistent treatment of VMPs and medicated feed. Registration of medicated feed should be granted for specific uses and may serve to restrict the use of medicated feed for certain non-veterinary medical uses, such as growth promotion, particularly where this is the case for other types of VMPs. Under *EU Regulation 2019/4,* the use of medicated feed that contains antimicrobials is prohibited for prophylaxis purposes under Article 17(3).

Specific authorization requirements may be in place for feed mills and other establishments that produce and sell medicated feed. Under *EU Regulation 2019/4,* the manufacture of medicated feed may only be carried out by approved manufacturers in approved establishments (Article 13). These facilities may be required to have systems in place that prevent the contamination of regular feed with feed containing antimicrobials. For example, this may be in the form of standards relating to cleaning methods, requiring

double production lines or other mechanisms to prevent cross-contamination. Similarly, medicated feed should be stored and transported in a manner that prevents cross-contamination with other medicated feed or with non-medicated feed.

Medicated feed may be required to be labelled in a manner similar to, or with elements of, VMP labelling, to provide the user with the information necessary to correctly administer the medicated feed. The advertising of medicated feed should be prohibited or subject to special restrictions coherent with the VMP provisions for advertising.

Legislation may prohibit the dispensing or sale of medicated feed without a prescription from a veterinary professional, and these professionals may be required to keep records relating to these kinds of prescriptions. In Canada, under the *Food and Drug Regulations (C.R.C., c. 870)*, a written prescription from a veterinary practitioner is required to sell medicated feed (C.08.012(1)).

Animal producers may also be required to keep records relating to the use and administration of medicated animal feed. In Viet Nam, the *Law on Animal Husbandry (2020)* requires animal feed users to keep a journal of the use of animal feeds containing antibiotics (Article 50).

An alternative to medicated feed is medicating the water served for the animals in question. When this is allowed by the national legislation, the regulatory framework should impose requirements relating to the administration and use of medicated water, similar to those for medicated feed. In addition, legislation should stipulate rules relating to effective cleaning of the system after treatment to ensure there are no antimicrobials left after treatment. FAO and WHO (2015a) also recommend that regulatory authorities should ensure the stability of antimicrobial drugs when they are mixed with water.

7.3. Pesticide management

Overview of key regulatory aspects of pesticide management relevant for addressing antimicrobial resistance

- The legal framework should cover all stages of a pesticide's lifecycle, and:
  - in addition to pesticides used for plants, the legal framework should cover pesticides used on animals and for public health;
  - where different authorities are responsible for different stages of a pesticide's lifecycle, legislation should establish mechanisms for coordination and collaboration between the authorities and the primary authority for pesticide management.
- It should be prohibited under law to manufacture, import, distribute, sell or use a pesticide that is not registered.
- The registration process may include broad decision-making criteria that allow consideration of the spread or development of antimicrobial resistance (AMR) as a factor in evaluation of the impacts on human or animal health or the environment.
- Registration provisions may include conditions or restrictions which may be allowed for the imposition of specific restrictions related to antimicrobial pesticides.
- The features of licensing and inspection systems (criteria for decision-making on location of facilities, operations and personnel) may be used to include AMR-specific criteria or conditions for issuance of a licence.
- Pesticide operators have record-keeping and reporting obligations under the law which facilitates the gathering of data on the quantity, distribution and use of antimicrobial pesticides.
- Legislative provisions relating to handling, labelling and use, enable particular provisions relating to the application of antimicrobial pesticides to be regulated and thereby prevent misuse and overuse.

Overview of key regulatory aspects of pesticide management relevant for addressing antimicrobial resistance *(cont.)*

- Provisions that promote alternatives to the use of pesticides, such as Integrated Pest Management, reduce the need for pesticides.
- Environmental accumulation of antimicrobial pesticides from manufacturing facilities or application can be minimized through regulatory tools such as impact assessments, special licences for aerial spraying and special licences for certain applications.
- Legislative provisions for the disposal of pesticides may mitigate AMR concerns that arise during transport (e.g. risks of spills and contamination with other products), and also following their use (e.g. discarding of leftovers in containers).
- Legislative provisions establishing the monitoring and data collection functions of the competent authority are useful to compile AMR-relevant data, and possibly to share with the national focal point for AMR surveillance.

7.3.1. Relevance of pesticide management for addressing antimicrobial resistance

Pesticides are utilized extensively for agricultural (crop and livestock) production and forestry management as well as for public health purposes, including pest and vector control. Antimicrobial pesticides (such as fungicides and antibiotics) or pesticides with antimicrobial effects (such as certain herbicides) may be used to control plant pests and are therefore regulated as pesticides. For the veterinary sector, externally applied pesticides such as antiparasitics or topical fungicides may (depending on the jurisdiction) also be regulated as pesticides. Streptomycin is considered the most widely used antibiotic for plant disease control worldwide, followed by oxytetracycline (Sundin and Wang, 2018). FAO estimates that antimicrobials used for crop production is relatively low, from approximately 0.2 to 0.4 percent of total agricultural consumption (FAO, 2020a). Nevertheless, a 2020 survey conducted by Taylor and Reeder using the Plantwise Online Management System revealed that all WHO regions are using antibiotics in plant production, with the exception of Africa (Taylor and Reeder, 2020). However, in the European Union, there is no antibiotic approved as an active substance for crop production, although some Member States authorize antimicrobials under the "emergency authorisation procedure" foreseen in Article 53 of *Regulation (EC) No 1107/2009* in order to combat pests for which no other means are available.

Research is pending on the extent to which antimicrobial pesticides used in crop production contributes to AMR with harmful implications for human health or animal health. Current research efforts on the impact of AMR via pesticides is limited by a number of challenges. Estimating the overall use of antimicrobials is made difficult by the fact that the number of countries currently monitoring the use of antibiotics in plant production is extremely low compared to those monitoring antibiotics use in the veterinary and medical arenas (FAO, OIE and WHO, 2018). In fact, based on current data, the impact of pesticides on AMR may be comparatively low. However, as some pesticides do contain antimicrobials, the presence of these substances in agricultural areas may create compounding effects in the environment where VMP residues or antimicrobial-resistant microorganisms are already present. Copper-based bactericides are very commonly used on a wide variety of crops, as these compounds represent one of the few bactericides in some countries. This leads to concern relating to the development of AMR in microorganisms and genes through the process of co-resistance, cross-resistance and co-regulation with certain metal ions. Evidence further indicates that contamination of soil with certain metal ions, such as copper ions, promotes AMR in soil bacteria (FAO and WHO, 2019)

7.3.2. Where are pesticides regulated?

Pesticides can be regulated under specific pesticide legislation, under general agricultural production or input legislation, or public health legislation (this is typically the case for household pesticides and pest control treatments, such as malaria). Some countries include pesticide provisions in general plant protection laws, or under general chemicals legislation. Veterinary pesticides may also be included under general veterinary legislation or possibly together with VMP legislation.

Different laws may cover various stages in the pesticide management lifecycle including: industrial or manufacturing laws; business licensing laws; advertising laws; consumer protection and product safety laws; and occupational safety or labour laws. Finally, various aspects of pesticide production, use and disposal (including the collection of pesticide waste), might be addressed in general environmental legislation, waste and hazardous waste legislation, pollution control laws, water laws or other environmental legislation.

7.3.3. Key regulatory stages of pesticide management relevant to antimicrobial resistance

It is recommended that the basic regulatory framework for pesticides is aligned with the *International Code of Conduct on Pesticide Management (ICCPM)*. The basic premise of this Section is that where the legislative framework is well-aligned with the ICCPM, it is already at a good starting point for addressing AMR, even without any AMR-specific language. The specific elements of pesticide legislation that are designed to minimize adverse health or environmental impacts can be strategic points at which AMR parameters can be introduced or considered by competent authorities. Subsequently, AMR-specific criteria, considerations and parameters can be added to, or subsumed within, a framework that is aligned to the ICCPM in the following ways: (i) implicitly as a result of broad phrasing in the text; (ii) through minor amendments in the primary text; or (iii) in subsidiary or lower-level instruments that are easily updated.

Regulatory controls to prevent AMR aspects can be considered at a number of stages in the pesticide management lifecycle. Under the ICCPM, "lifecycle" is defined to mean "all the stages a pesticide might pass through from production to its degradation in the environment after use, or its destruction as an unused product. The lifecycle includes manufacture, formulation, packaging, distribution, storage, transport, use and final disposal of a pesticide product and/or its container." However, regulatory frameworks may control pesticides that have antimicrobial effects primarily in two key ways: (i) by prohibiting, restricting or limiting the use of such pesticides (during such stages as registration, distribution and use); or (ii) by requiring additional guarantees in the *manner* of the use of such products. How these restrictions and requirements are developed in legislation will be explored below.

Definitions and scope

The ICCPM defines a pesticide as "any substance, or mixture of substances of chemical or biological ingredients intended for repelling, destroying or controlling any pest, or regulating plant growth" (Article 2). This definition, which encompasses pesticides for all types of uses – crop protection, veterinary use and public health use – also includes antimicrobials and substances with antimicrobial effects. Legislation may establish the scope as applying to only one of these sectors and there may thus be gaps or fragmentation of the legal framework for pesticides in the country. Furthermore, pesticide legislation should designate the competent authority for pesticide management in the country, although it is possible that various authorities have responsibilities along the lifecycle. The relevant authorities include the ministries responsible for agriculture, for health, or for the environment, or alternatively, may be a separate body (Section 4.2 of the *ICCPM Guidance on Pesticide Legislation*). What is important for effective coverage of the entire lifecycle is

coordination among authorities and mechanisms for cooperation with public and private stakeholders for such purposes. The ICCPM recommends that all pesticides be regulated together, including chemical and biological pesticides for agriculture (for livestock or plants) or pest control (for public health purposes). Typically, MRLs of pesticides in food and feed are regulated under food safety legislation (see Section 8.1 of this Study).

Registration

Legislation typically prescribes that no pesticide should be placed on the market unless it is registered as prescribed. More generally, all pesticides are only recommended to be registered following a risk-analysis based procedure that takes into account environmental, human health and agronomic considerations (Articles 5.1.1, 6.1.4, 6.1.5, 7.3 of the ICCPM). Legislation may stipulate data requirements to be included in registration dossiers, and should also include decision-making criteria to enhance transparency in decision-making (Section 4.3.3 of the *ICCPM Guidance on Pesticide Legislation*). In Vanuatu, according to the *Pesticides (Control) Act 1993 (Cap. 226),* no person shall import, manufacture, formulate, pack or distribute, sell, offer for sale or offer as a gift any pesticide, unless such pesticide is registered and a certificate of registration is obtained under the Act (Section 8). The Act also identifies the particulars that should be included in the registration application, such as toxicological data, the breakdown of product substances and information on its environmental impact (Section 10).

These provisions may allow for the inclusion of AMR-specific data to be submitted for evaluation and be a condition of registration. In this way, AMR considerations may be included as one of the decision-making criteria during the process of registration. Registration may prohibit pesticides on the *WHO List of Critically Important Antimicrobials for Human Medicine* that are declared "critically important" (such as streptomycin), as well as restrict others that are "highly important" (such as tetracyclines). Alternatively, registration may restrict these antimicrobials for emergency use only (and registration conditions may impose strict control over the use of these substances, such as special licensing or reporting duties). Legislation may state that registration may impose any specific restrictions or conditions in relation to the product, including on handling and application. In terms of the legal framework, even a general stipulation to assess the pesticide on human health or other grounds serves as sufficient legal basis for regulators to incorporate AMR-specific parameters in the actual evaluation and technical decision-making processes, particularly where these are set out in lower-level instruments that are easily modified. For example, the *Pesticides Act (1987)* in the Cook Islands requires a registration applicant to demonstrate a specific need for the proposed pesticides in the Cook Islands as well as to show that the use of the pesticide would not give rise to an unacceptable hazard to the public or the environment (Section 12). Antimicrobial pesticides that may demonstrate limited environmental or residue build-up, limited AMR impact or that may be preferable than other types of pesticides in the risk assessment process may also benefit from fast-track registration procedures.

However, some countries have created a specific distinction for *antimicrobial* pesticides and have imposed explicit additional regulatory burdens for these types of pesticides. In the United States, "antimicrobial pesticides" are, in addition to the requirements imposed on conventional pesticides, subject to additional registration requirements, and defined in the *Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) 7 U.S.C. §136 et seq. (1996)* as "a pesticide that – is intended to – (i) disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms."

Legislation provisions for re-registration once the initial registration period has expired, provides an opportunity to re-examine the grounds that led to registration in the context of new evidence and data on AMR risk and effects, or changes in AMR policy. In Eswatini, under the *Pesticides Management Act (2017)*, an application for the renewal of the registration of a pesticide can be made to the Registrar at least thirty days prior to the expiry of the validity of the registration. At this stage, the Registrar can require new information

to support the renewal (Section 24). A similar mechanism is the obligation of the competent authority to periodically review registrations that are in force, and either suspend or cancel registrations where new information demonstrates risks to humans, animals or the environment (Article 6.1.9 of the ICCPM). This allows for the constantly evolving data on AMR-specific risks that may come to light in the period since registration, to be considered in the review.

Other AMR-related considerations may be triggered at the registration stage. The specific label of the product or safety data sheets are decided at registration, and for relevant pesticides appropriate pre-harvest intervals may be indicated. The legislation should prohibit changes to the approved label without the permission of the registration authority (Section 4.3.4 of the ICCPM *Guidance on Pesticide Legislation*). Antimicrobial pesticides like other pesticides should have MRLs set at this stage (which are then monitored in food), thus AMR considerations can be made at this point too.

Pesticide laws typically establish a pesticide registration entity that is responsible for technical or final decision-making on registration. In accordance with good practices, this entity should encompass authorities from all stages of the pesticide lifecycle, to ensure broad representation and consideration of the disciplines relevant for risk assessment. Such registration bodies are therefore well-placed to examine any human-animal-environmental concerns, such as AMR.

Licensing

Licensing systems established by law enable the competent authority to retain oversight on various parts of the pesticide lifecycle, including operations, facilities (location, design, processes, etc.) and the licensed persons and their staff (i.e. their skills or experience). Licences may typically be required for manufacture, formulation, import, export, sale or distribution, storage, transport, commercial application (e.g. fumigation) and special uses, such as the use of certain Highly Hazardous Pesticides, aerial spraying, and disposal. In Malawi, under the *Pesticides Act (Cap. 35:03, last amended 2012)* a licence is required for manufacturing, exporting, distributing, storing for sale or selling a pesticide (Section 24). Licence holders are generally required to comply with the conditions of their licence and an inspections system is usually set up to monitor compliance with regulatory requirements. The decision-making processes for the issuance of licences usually requires consideration of the potential hazards associated with the pesticides produced, handled or distributed by the licensees. Countries may decide, for instance, to require that the sale of a pesticide is accompanied by the necessary protective gear. Where legislation lists the grounds for the issuance of the licence, (i.e. where the law sets out specific requirements to be met relating to the operations, processes, facilities and personnel), these features of licensing provisions allow for the inclusion of AMR-specific controls and considerations. Licensed operators are often obligated to keep records and report certain data (Article 6.1.10 and 6.1.11 of the ICCPM), and this offers an important avenue for gathering data on the number of antimicrobial pesticides produced, sold and used.

Under Article 5.2.5 of the ICCPM, Licence holders may be required to stop sale or distribution, or to recall products whose registration has been suspended or cancelled or because the product presents an unacceptable risk.

Labelling, handling, storage and use

Legislation should prohibit the sale of pesticides that do not bear the approved label. Legislation may prescribe the information to be provided on the label and the features of such label (Article 5.2.4.7 of the ICCPM, and the *Guidance on Good Labelling Practice for Pesticides*). Pesticides should be labelled in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and should include directions for use, hazardous information, precaution measures, pre-harvest interval, and

other matters confirmed during registration (UN, 2011). Article 3.5.4 of the ICCPM states that information should be provided in one or more of the country's official languages and in a suitable format to ensure effective use, and minimize risks to users, the public and the environment. As labels generally contain information on the ways the pesticide should be used, stored and handled, appropriate labelling may mitigate the risks of misuse or overuse of antimicrobial pesticides or pesticides with antimicrobial effects. Cambodia, in *Law on the Management of Pesticides and Fertilizers (2012)*, contains labelling requirements such as technical instructions on the mode of use, target crops and target pests, recommended dosage, time of application and pre-harvest intervals, instructions on detoxification, and safety measures for the disposal of pesticide waste and used containers (Article 22). These labels are required to be in the Khmer language (Article 23).

Even antimicrobial pesticides that were registered following a rigorous review process may contribute to the development of AMR where not properly handled, used or disposed. Improper use may also create resistance to pesticides generally, which reduces efficacy, and in turn results in the need for the application of greater volumes, concentrations or strength of the product. Improper use also includes not observing pre-harvest intervals between application of the pesticide and harvest or withdrawal periods. Pesticide handling and use should be compatible with existing levels of users and expertise, and as these vary widely from country to country, availability and use decisions are left to the discretion of each government (Article 7.1 of the ICCPM).

From an AMR perspective some of the main requirements relating to labels include: product content information such as the product name, product category, active ingredient name and concentration; hazard and safety information; directions for use including field of use (target crops/pests); dosage; mode of application; personal protection; pre-harvest intervals; storage and disposal instructions; and the supplier identification and contact number.

Use, handling or application of pesticides may be prohibited if not in accordance with the label instructions and the safety data sheet. Certain classes of pesticides may be restricted for use except for authorized persons (such as commercial applicators) with the necessary qualifications and equipment to handle these classes of hazardous pesticides. In Ethiopia, the *Pesticide Registration and Control Proclamation (No. 674/2010)* establishes a class of restricted use pesticides, which are determined by the ministry to be unsafe for use by persons not holding a certificate of competence (Section 2). The Pesticides Board is further tasked with establishing requirements for the handling of such pesticides (Section 28).

Laws on pesticides often set out specific rules relating to storage and transport, with the key purpose of avoiding spills and accidents and contamination of the environment. Furthermore, pesticides are required to be stored and transported in such manner as prevents contamination with food or other prescribed items, and restricted proximity to persons and animals. Storage spaces should meet prescribed construction, design and layout standards. Pesticide warehouses may be prohibited from being located near residential areas, water bodies, protected areas, forests, food processing facilities or livestock facilities. This is the case for example in the United Republic of Tanzania, where the *Plant Health Act (No. 4 of 2020)* prohibits the storage of pesticides inside the same premises as food products, consumables, feedstuffs or animals. Storehouses for pesticides cannot be located near hospitals, schools, shops, densely populated urban areas, protected areas or water bodies (Section 51).

Legislation should require employers of workers who handle pesticides to ensure training and awareness of their staff on the risks associated with handling those types of pesticides. Employers must ensure appropriate application equipment is provided for staff, including personal protective equipment, and should also be required to ensure the appropriate cleaning of application equipment, and safe disposal of empty containers. In Section 23 of the Botswana *Agrochemicals Act (Chapter 35:09, 1999)* an employer is required to provide

to his or her worker such facilities and clothing to ensure both the safe handling and use of agrochemicals (including pesticides).

The FAO *Guidelines on Prevention and Management of Pesticide Resistance* highlight how the improved use of integrated pest management (IPM) can reduce risks associated with pesticide resistance, and thus may be a useful illustration of how IPM and other related alternatives can be used to address AMR. The role of the extension services for crop production or other field-level public health or veterinary level staff, contribute to securing widescale compliance with good practices and with increased use of alternatives to antimicrobial pesticides. The competent authority may promote practices such as IPM. The IPM approach reduces the need for pesticide use (these chemicals are used only when necessary) and promote use of alternative pest management techniques by minimizing the selection pressure that leads to resistance (FAO, 2012). Part of this approach includes a comprehensive Resistance Management Plan tailored specifically to the pest, the crop and the region (FAO and WHO, 2019). Other important complements include, for agriculture, the application of biocontrol and adoption of disease-resistant crops, and for animal health and public health, good hygienic practices. This would include not only pest prevention and reduction, but also awareness-raising on the correct handling, use and disposal of pesticides.

Environmental aspects and disposal

Challenges relating to pesticide build-up or dispersal in the environment, or entry in the food chain entail risks to human health and animal health, not only owing to the hazards associated with pesticides *per se*, but also AMR-specific risks too.

As regards mitigating environmental externalities, pesticides or environmental legislation may refer to general environmental laws or contain specific references to environmental impact assessments (see Section 8) and environmental impact mitigation, particularly for facilities for manufacture or formulation, or for warehouses.

Specific restrictions or prohibitions may apply near water bodies, such as the prohibition of aerial spraying or the duty to apply pesticides at least a certain distance from the water body.

Accident and incident reporting systems may create a structure for ensuring 'multi-sectoral coordination of different authorities. This enables a prompt clean-up where required as well as continuous coordinated data gathering.

Disposal

Possible AMR risks are created during the disposal of antimicrobial waste, either at manufacturing facilities, during transport (e.g. risks of spills or contamination with other products); following use (e.g. leftovers); or other types of dispersal into the environment (including the discarding of pesticide containers). Legislation may offer various mechanisms to facilitate the safe management of antimicrobial pesticide waste and disposal of obsolete and unused pesticides and pesticide containers. First, it is necessary to identify the authority responsible for ensuring the disposal of pesticide waste and containers, given that a number of laws (environmental laws, chemicals laws, agriculture laws, hazardous waste laws, etc.) may establish a mandate to different authorities for the disposal of this type of waste. The responsible authorities are usually those relevant to AMR responses (environment, agriculture, health). Thus, provisions for coordination, cooperation or collaboration are needed, with oversight on pesticide disposal to be undertaken by the competent authority for pesticides.

Legislation may also stipulate that the disposal methods should be established by the competent authority. This provides an opportunity to introduce specific methods for the disposal of antimicrobial pesticides. Any spills or other emergencies related to pesticides are often required by law to be immediately notified to the competent authority for pesticides. Any person who sees illegal dumping of pesticides, or who discovers

a dumping site, is obligated under law to notify the competent authority or the local police. Legislation should prohibit: the pouring of pesticides down drains or into water sources or drainage channels; the burying of pesticide-related waste; the disposing of pesticide-related waste in general landfills without prescribed rinsing, instead of disposing in approved landfill sites designated to prevent contamination; and the burning of pesticide-related waste unless in an approved incinerator (FAO and WHO, 2020b, Section 4.10). These provisions would also apply to antimicrobial pesticides but can also be modified and adapted to address antimicrobial-specific impacts or effects.

Legislation may also impose obligations on sellers to receive back any unused or obsolete pesticides or empty pesticide containers, as part of a collection scheme for sound disposal. As an example, the *Pesticides Act of Bhutan (2000)* provides for the right of farmers to return obsolete pesticides to the seller of such pesticides. The seller shall then submit the returns to the Board, as prescribed (Section 21).

Pesticide dealers may establish purchasing procedures to prevent oversupply. Alternatively, dealers may enter into arrangements or partnerships with local government or third parties to collect empty containers. The competent authority may establish specific standards and protocols for the safe disposal and management of pesticide waste by authorized persons.

Data collection and exchange, and related activities

The ICCPM recommends the use of all possible means to collect reliable data and record statistics on environmental contamination and adverse effects, and report specific pesticide-related incidents. Data collection enables the quantification of the actual risks of use, in a manner that is specific to the country context. This facilitates an understanding of the drivers of AMR in general (and specifically in plants) and therefore can influence the design of regulatory interventions to address AMR.

The competent authority for pesticide management may be empowered to gather and analyse data relating to pesticides. Legislation often imposes a corollary duty on operators in terms of keeping records and reporting obligations. Articles 6.1.10 and 6.1.11 of the ICCPM requires pesticide operators to keep records for a specified time period, to make their books and records available for inspection at all reasonable times, and to report any incidents of health problems or environmental contamination resulting from pesticide use to the competent authority for pesticide management. Thus, routine and special inspections carried out by the competent authority during all stages of the pesticide lifecycle offer potential data sources. Through these provisions, the authority may gather specific data relating to antimicrobial pesticides as well as the types of pests or diseases that necessitate antimicrobial therapy. Data can also be gathered on incidents that may create a risk for the spread of AMR. Unless there are restrictions on the sharing of data among public institutions, data may be shared with the AMR focal point, ministry of health or other body responsible for AMR monitoring and surveillance.

8. Preventing contamination of the food chain and the development and spread in the environment

8.1. Antimicrobial resistance in the food chain

8.1.1. Relevance of food safety for antimicrobial resistance

There are multiple pathways for antimicrobials to enter the food chain and result in the development and spread of AMR in humans. One of the pathways is the consumption of food that may be contaminated with microorganisms that have gained resistance to antimicrobials, and thus exposes humans to AMR microorganisms (Cahill *et al.,* 2017). Raw foods typically have the highest microorganism concentrations, followed by minimally processed foods and subsequently, fully processed foods. The consumption of certain antimicrobial-resistant microorganisms may also become a source of transferable resistance determinants for other microorganisms, including human pathogens (FAO and WHO, 2023c). Another pathway is via residues from pesticides found in crops, from VMP residues or from feed containing antimicrobials found in foods of animal origin. While antimicrobial-resistant microorganisms and antimicrobial residues are food safety hazards, the actual risks vary among different microorganisms as well as in different regions (FAO and WHO, 2023c).

Food safety legislation governs activities to ensure the safety (and quality) of food along the entire food chain (including primary production, handling, storage, processing, distribution, food services and consumption), integrated with preventive and educational strategies (FAO and WHO, 2019). The premise of this Section, as with Section 7, is that a robust framework that complies with international standards is conducive to prevent the development and spread of AMR through the food chain. As stated in the Codex *Principles and Guidelines for National Food Control Systems (CXG 82-2013),* legislation should follow the entire food chain approach so that it applies to all food businesses at all stages of production and distribution, including the production of farm inputs such as feed for food producing animals (i.e. the "farm-to-fork" approach). Animal feed safety comprises the early parts of the food chain which is included in food safety legislation and as such, feed products for food-producing animals may be subject to the same residue monitoring requirements and control mechanisms as food products.

Food hygiene practices form an essential element for the control of AMR, by controlling microbial populations that harbour the AMR gene pool (Cahill *et al.*, 2017), and by limiting the impact of drug-resistant infections by breaking the chain of transmission (O'Neill, 2016). Accordingly, countries that have strong food safety control systems that comply with Codex standards provide a strong basis from which to address antimicrobial challenges. This Section 8.1 contains some of the key elements of a modern food safety system based on international reference standards and best practices. Notwithstanding, as this Section 8 is not intended to offer a complete review of the legal framework for food safety, it is noted that other resources are more suited for this purpose. Specifically, the FAO/WHO Food Control System Assessment Tool (FCSAT) can be

used to evaluate a country's entire food control system.[9] Section 8 canvasses only the parts of the food control system that may offer ways to prevent the (currently understood) AMR risks in the food chain.

8.1.2. Where is food safety regulated?

Food safety can be regulated in stand-alone food safety (and quality) laws, in public health codes, or in combined food and drugs legislation. Provisions relating to food safety and quality could also be housed in laws governing general consumer protection, standards, import and export, business laws or agriculture laws.

The power to establish MRLs may be found in various laws (food safety, public health, etc.), while the MRL itself is often established through food standards or subsidiary legal instruments.

8.1.3. General features of the food safety control system

Overview of general features of food safety systems relevant for antimicrobial resistance

- The legal framework for food safety should encompass all stages of the food chain from farm-to-fork, and a clear delineation of mandates of the responsible authority/authorities is necessary. In the case of multiple responsible authorities, the legal framework should:
  - establish the single entity that has final responsibility for food safety;
  - include mechanisms for coordination in the case of multiple responsible authorities – because these authorities often involve those responsible for addressing antimicrobial resistance (AMR), coordination mechanisms provide a strategic avenue to address the multidisciplinary dimensions of food safety related aspects of AMR.
- Legislation should establish the primary responsibility for food safety with the food business operator (FBO) that produces/manufactures/distributes the food, and FBOs may be monitored by the competent authority through:
  - licences-to-operate, or registration requirements;
  - periodic inspections.
- Legislation should empower the competent authority to establish food safety standards and requirements (in line with international standards); these are strategic entry points that allow for the inclusion of AMR-specific parameters and considerations.

Definitions and scope

The scope of the legislation may depend on how "food" is defined. The *Codex Alimentarius* definition of food (see Section 3.2), covers any substance directly or indirectly intended for human consumption including ingredients, raw materials, and drink. Thus, aspects relating to the contamination of water with antimicrobials, and antimicrobial-resistant microorganisms are also a consideration.

Institutional frameworks and food safety mandates

One of the fundamental requisites of a well-functioning food safety system is coordination of regulatory authorities to ensure complete coverage from production to consumption (i.e. the farm-to-fork continuum), without fragmentation of responsibilities that could create gaps or overlaps. Where a number of entities

9 The FCSAT can be accessed at https://www.fao.org/food-safety/food-control-systems/assessment-tool/en

are involved along the food chain, or even where a single agency is identified as the competent authority, it is important that the *overall* supervision or coordination rests with one body (CXG 82-2013). Where there are overlaps of functional mandates, coordination and collaboration prevents those overlaps from resulting in duplicated enforcement and implementation. In this way, AMR considerations that fall under the authorities that are responsible for various parts of the chain may be addressed and coordinated.

Legislation should set out the specific mechanisms for coordination if there are multiple authorities, for example a (multi-stakeholder) standards-setting committee, or a coordination or policy committee. This approach brings together expertise from both animal health and food safety, and to a lesser extent environment, and could encompass mechanisms for notification and reporting of threats and hazards, record-keeping and the exchange of information (including inspection results) between authorities. The use of MoU or similar instruments may, where allowed in the jurisdiction and where underpinned by legislation, set out the details for collaboration (i.e. the breakdown of specific roles). Regardless of the modality of coordination, the mechanisms may include AMR aspects in the text of a coordination instrument or in the mandate/discussions of a coordination body.

Food safety laws often empower the competent authority to regulate specific aspects of food, for instance hygiene, labelling, advertising, additives, adulteration and contamination. Therefore, the competent authority has a clear basis to approve food safety measures (including laws and standards) to prevent, identify and control food hazards. In Antigua and Barbuda, the *Food Safety Act (2020)* empowers the Food Safety Service to establish a risk-based food safety and quality framework to protect, enhance and ensure food safety and to protect consumers from food fraud, and provides them with a long list of competences, including prohibiting or setting limits for food additives usage, pesticide and veterinary drugs, residues, contaminants, and other substances (Article 6).

Food safety measures should be based on *Codex Alimentarius* standards. This provides an opportunity to include antimicrobial contamination in the parameters of such measures. In this regard, the Codex CXC 61-2005 is a key international reference document to manage risks to human health associated with antimicrobials (and antimicrobial-resistant microorganisms) in food and feed. Food safety standard-setting may be undertaken by designated bodies and may be issued through various types of instruments ranging from legally binding regulations to technical standards. The National Codex Contact Point often has a role in the development of national food safety and quality standards.

The competent authority should be empowered to carry out risk assessments regarding the safety of food for human consumption, as well as to manage and communicate risks. Relevant guidance may be found in *Guidelines for Risk Analysis of Foodborne Antimicrobial Resistance (CXG 77-2011)*. Competent authorities should consider results of foodborne AMR risk assessments to identify potential sources of AMR development in the food production environment.

As food safety hazards emerge and evolve constantly, it will not be possible to have every conceivable issue anticipated by the law. Therefore 'catch-all' provisions that can be used to address a range of food safety hazards and offer legislative entry-points under which to address risks arising from antimicrobials and antimicrobial-resistant microorganisms. Examples include phrasing such as "food that is potentially injurious to health", "unsafe food" or "food that is unfit for human consumption", etc. These terms could in principle include food that contains antimicrobials above a certain threshold or antimicrobial-resistant microorganisms.

Food business operators (FBOs)

Usually a food business operator (producer, manufacturer, transporter, retailer, etc.) bears the primary responsibility for ensuring that food within their responsibility is safe (CXG 82-2013). Antigua and Barbuda's

Food Safety Act (2020) explicitly places the primary responsibility for ensuring the safety of food on FBOs (Section 32).

Registration or licences-to-operate issued by the competent authority for food safety offer mechanisms by which FBOs are controlled. Typically, applicants must demonstrate they are able to meet safety and hygiene requirements in order to continue to do business. Food safety control systems also promote awareness-raising initiatives as well as mandatory training of food operators in food handling for hygiene and safety of food. In Nauru, the *Food Safety Act (No. 4 of 2005*) requires that all food handlers undergo training offered by the health authorities or by a training organization accredited by the health authorities (Section 10) prior to commencing work in a food business. These AMR-specific conditions or requirements may be imposed on FBOs through regulatory requirements and tools.

8.1.4. Maximum residue levels

Overview of key regulatory elements for maximum residue levels relevant for addressing antimicrobial resistance

- Legislation should require the setting of maximum residue limits (MRLs) for pesticides and veterinary drugs/ veterinary medicinal products in food.
- Legislation should clearly identify the entity that will issue the MRL and the entity that will monitor compliance/ ensure enforcement of the MRL.
- Legislation may expressly prohibit the sale of food that exceeds the established MRL.

Rationale

The consumption of foods originating from animals that have been treated with VMPs may be a source of exposure to antimicrobials as well as antimicrobial-resistant microorganisms, particularly where the withdrawal period between treatment and slaughter/harvesting has not been observed. In addition, carry-over from feed to food may also serve as a pathway for entry of antimicrobials and resistant-mircoorganisms into the food chain (FAO and WHO, 2019). The residues of pesticides may be toxic to humans above a certain threshold, and antimicrobial pesticide residues above a certain amount may contribute to the development of AMR in the food chain.

Requirements

Legislation may require the establishment of MRLs for all authorized VMPs as well as for pesticides used for food and feed crops. The setting and re-evaluation of MRLs enables AMR-related risks to be factored. The *Codex Alimentarius* defines MRLs for pesticides and for veterinary drugs (FAO and WHO, 2018).

Regarding pesticides, MRLs have been established by the CAC for a large number of substance-crop combinations, and default MRLs may apply to substance-crop combinations for which there is no MRL. The process of setting an MRL for a pesticide is related to the screening process undertaken during the registration stage of the pesticide's lifecycle (see Section 6.3 of this Study) – account is taken of residues found on crops treated with the pesticide under conditions of good agricultural practices (GAP). Products for which no MRL can be set should not generally be authorized for use on crops for food or feed. As mentioned, products not authorized in one country may be authorized in another country, for example,

for reasons of climatic differences. For such products, MRLs (also known as import tolerances) should be set or a default MRL used in order to bridge any remaining gaps.

Regarding VMPs, an MRL should be set for all authorized antimicrobials, and in deciding the appropriate level, whether or not the residues are still pharmacologically active, is relevant for determining whether the residue would contribute to the spread of AMR.

It is important to determine which entity has the mandate for *establishing* or *approving* MRLs for VMPs and pesticides. This could be a specialized food safety authority, the public health authority, or the livestock or crop authorities in collaboration with the former. *Enforcement* of MRLs takes place through inspections or reporting requirements. In some countries, the standards may be issued by one entity, but inspections, monitoring, surveillance and enforcement may be carried out by another. Regardless of the actual entity responsible for a task, effective coordination throughout the food chain will require the sharing of information, sharing inspection and monitoring results, and generally cooperating to ensure safety at all stages of the food chain.

Regarding standard setting, the competent authority often approves food safety and quality standards based on Codex standards. For example, under the US *Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301-399d)*, the Administrator of the Environmental Protection Agency is tasked with setting MRLs for pesticides in food, and in so doing must first determine whether an MRL for the chemical pesticide has been established by the Codex Alimentarius Commission. If such a Codex standard exists, and the Administrator does not propose to adopt it, they are required to publish a notice for public comment explaining the reasons for departing from the Codex standard (Section 408). Tanzania's *Fisheries Regulations No 308 of 2009* establishes control of aquaculture practices (Regulation 39) which include ensuring that the VMP residue in harvested fish does not exceed the established MRL. Furthermore, live fish shall not be sold prior to the completion of the withdrawal period where such fish has been treated with VMPs. Also, VMPs should not be used to treat fish except in accordance with practices established by the competent authority. It is illegal to import or distribute fish which exceed the permissible level of additive or VMP (Regulation 93). Another example is Georgia's *Resolution No. 22 of 2016 on Measures to Monitor Certain Substances and Residues thereof in Living Animals and Animal Products,* which sets principles regarding certain substances in food of animal origin and provides rules for periodic monitoring of these substances. Specifically, monitoring is undertaken for substances of anabolic effect, prohibited substances, and veterinary drugs and contaminants. The Resolution also provides for the duties and rights of the National Food Agency of Georgia with respect to the monitoring of MRLs; obligations of veterinarians; obligations of FBOs; requirements relating to laboratory analysis of residues; monitoring during slaughtering; and taking samples from animal products including from specific animal products (milk, eggs, wild animals, honey etc.).

8.1.5. Microbiological criteria

Overview of key regulatory elements for maximum residue levels relevant for addressing antimicrobial resistance

- The setting of microbiological criteria in pathogen-product standards by the competent authority should be complied with by the food business operator (FBO).
- Legislative provisions for inspections provide the basis for sampling and testing to monitor compliance with the microbiological criteria.
- Legislative provisions regarding the shelf-life of a product (e.g. labelling rules that include expiry dates, description of storage conditions, etc.) enable food to remain within the permitted microbiological criteria.

Rationale

Microbiological criteria (MC), which give appropriate indicators for microbiological limits, can be used with regard to food products or processes/control systems to determine the maximum levels of microorganisms. Thus, the setting and enforcement of microbiological criteria can be used to prevent the spread and development of AMR through antimicrobial-resistant microorganisms.

Requirements

Legislation should establish limits on the presence of commensal microorganisms in food throughout its shelf life. In *Principles and Guidelines for the Establishment and Application of Microbiological Criteria Related to Foods (CXG 21-1997)*, the CAC defines microbiological criteria as a "risk management metric which indicates the acceptability of a food, or the performance of either a process or a food safety control system following the outcome of sampling and testing for microorganisms, their toxins/metabolites or markers associated with pathogenicity or other traits at a specified point of the food chain" (CXG 21-1997, p. 1). Although specific numbers for pathogen-product combinations are not directly established in CXG 21-1997, the CAC provides principles to guide competent authorities in setting such criteria for pathogens of concern and for determining the risk that such pathogens pose to consumers (humans, or animals in the case of feed). In setting the numbers for pathogen-product combinations, competent authorities must also look at vulnerable parts of the population (such as immune-compromised persons, the elderly, children and pregnant or lactating women). Competent authorities may monitor and control microbiological criteria through inspections systems. Subsidiary legislation or inspection manuals may set out the methods to be used, including a sampling plan, by which to assess the level of pathogens in the food.

However, it is incumbent on the FBO to ensure the food distributed is within the established microbiological criteria. In the Cook Islands, the *Food Regulations (No. 01 of 2014)* states that all food products for sale must comply with the microbiological criteria established by the *Codex Alimentarius* and as specified in the Regulations, and this provision is strengthened by a specific requirement for FBOs importing or processing food to be responsible for complying with these microbiological criteria (Article 11). To this end, the Codex CXC 61-2005 encourages FBOs to refer to the Codex *Principles and Guidelines for the Conduct of Microbiological Risk Management (CXG 63-2007)*. In determining the shelf-life of food (best before date, expiration date or use-by date as the case may be), FBOs should consider the possible presence and likely outgrowth of the microorganisms under normal storage conditions. Expiry dates should be made visible on the package or label, along with most appropriate conservation methods (e.g. requirement of refrigeration) and other information to maintain the safety of the food.

8.1.6. Food hygiene

Overview of key regulatory elements of hygiene relevant for addressing antimicrobial resistance

- Legislation should establish food hygiene requirements for primary production, as well as for processing to minimize the presence of antimicrobials and antimicrobial-resistant microorganisms.
- Detailed practices on hygiene may be found in subsidiary or non-legislative instruments on good agricultural practices, good hygienic practices and good manufacturing practices.

Rationale

Ensuring food hygiene is important to prevent contamination of food with microorganisms, including antimicrobial-resistant microorganisms, as well as residues of antimicrobials. Hygienic controls play a crucial role in minimizing these vectors, as food contamination may also occur when food is handled or exposed to the environment (Cahill *et al.,* 2017). The food safety objectives of preventing spoilage and illness are evident, as are the objectives to prevent these potentially resistant microorganisms passing through to the consumer. Less evident however is that antimicrobials may sometimes be used in food preparation for these same purposes.

It should also be noted that waste contaminated with antimicrobials from food products or food production may result in the dispersal of antimicrobial-resistant microorganisms and antimicrobial residues in the environment (see Section 8.2 of this Study).

Requirements

Legislation typically stipulates that food should be produced and handled in such a way as to ensure food hygiene and minimize the introduction, presence and growth of microorganisms. Vanuatu's *Food (Control) Regulation (No. 37 of 2007)* requires that all steps in the food production process need to be performed under conditions which will prevent the possibility of contamination or deterioration of the food through the introduction and growth of pathogenic and spoilage microorganisms (Article 43).

The FBOs have primary responsibility for ensuring food hygiene and ultimately ensuring that food (and feed) is safe and fit for consumption. The Codex CXC 61-2005 emphasizes practices to reduce the need for antimicrobial agents. Accordingly, legislation may require or incentivize the use of alternatives, such as heat treatment of foods, including pasteurization and sterilization, high-pressure processing (cold pasteurization), pulsed electric fields and irradiation, as referred to in the Codex texts *General Standard for Irradiated Foods (CXS 106-1983)* and *Code of Practice for Radiation Processing of Food (CXC 19-1979)*.

In legislation, operators may be required to implement a food safety management system. While this term usually refers to ISO 22000:2005, which is a certification standard that combines the generic management system of the ISO 90011:2000 group with the hygiene requirements of the food industry under the Hazard Analys is and Critical Control Point (HACCP) System, it can also be a generic reference to an overarching quality assurance system. The *Papua New Guinea Standard for Fish and Fishery Product* requires all licensed operators to document, maintain and implement food safety management policies relating, but not limited to, capture, harvest, transportation, landing, processing, storage and dispatch of fish and fishery products (Article 12.11). In countries where it is feasible, quality assurance systems such as the HACCP may be mandatory. The HACCP is a quality assurance system for food products that identifies, evaluates and controls hazards. It comprises seven principles: (1) hazard analysis; (2) critical control point identification; (3) establishment of critical limits; (4) monitoring procedures; (5) corrective actions; (6) record-keeping; and (7) verification procedures.

For primary food production, which is defined in Codex CXC 1-1969 as "those steps in the food chain up to and including, for example, harvesting, slaughter, milking, fishing" (Rev 4-2003), the hygiene elements to ensure fitness and wholesomeness of food are often set out in manuals or guidelines for good agricultural practices (GAP), rather than in laws. The GAP guidelines address how livestock or fish are fed (i.e. feed controls), how they are raised and treated with VMPs, and the observation of withdrawal periods. As water for both human and animal consumption and other drinks are included in the Codex Alimentarius's definition of "food", environmental contamination concerns are also a consideration.

Similarly, hygiene elements for processing are set out in manuals or guidelines for good hygiene practices (GHP) or good manufacturing practices (GMP). According to the Codex CXG 82-2013 Guidelines, legislation may establish the basis for GAP, GHP or GMP and may make explicit what these practices mean to different FBOs. In Zambia, a legal basis for the minister who is responsible for food safety to establish GMP, GHP and HACCP is granted by Section 37 on the regulatory powers of the minster under the *Food Safety Act (No. 7 of 2019)*. The objectives of GMP are to control the changes caused by reactions during the manufacturing and processing of raw materials (that result in changes in composition, nutritional value, physical structure and sensory properties), and by controlling these changes, develop the desired qualities in the product, to ensure food safety and to stop or slow down deterioration in the food. Basic guidelines for GHP follow the Codex CXC 1-1969 Principles, and include requirements for the design of facilities, control of operations, maintenance and sanitation, personal hygiene and training of personnel. The GHP covers processing, handling, transport and distribution procedures. As mentioned in other sections, the CAC has established several codes of hygiene practice for selected commodities, including the *Code of Practice on Good Animal Feeding (CXC 54-2004)*.

8.1.7. Traceability, recall and emergencies

Overview of key regulatory elements of traceability, recall and emergencies relevant for addressing antimicrobial resistance

- Legislation may require all food that is sold to bear a label containing prescribed information such as labelling in a language commonly understood in the country and instructions for storage, preparation, and use.
- Legislation may establish systems for traceability and recall, which enables (potentially contaminated or unsafe) food and ingredients to be traced at any stage of the food chain, and under which:
  - the food business operator (FBO) is required to keep records one-step-forward and one-step-back;
  - the authority may require a recall of products or undertake the recall directly if not implemented by the FBO;
  - recalled products should be disposed of in the manner prescribed by the competent authority.
- Legislation may contain provisions that allow the competent authority to respond to circumstances that rise to the level of a food safety emergency and may require the preparation of emergency response plans which bring together multiple stakeholders to enable a coordinated response.

Rationale

A food that is found to create an unacceptable risk, whether because of microbiological or antimicrobial contamination, the presence of highly resistant microorganisms or other factor, should be recalled from the market (through a traceability system). Where there is an outbreak of a foodborne illness or the risk is otherwise significant, emergency procedures may be required. Exposure of consumers must be limited as much as possible.

Requirements

All FBOs are responsible for any incidents associated with the foods (or ingredients) they distribute. Legislation requires FBOs to be issued with a unique business identification/registration number; ensure foods are labelled in accordance with requirements; and keep records – all these requirements comprise integral parts of the recall and traceability systems that are overseen by the competent authority. Botswana's *Food Control (Food Safety Alerts and Food Recall Procedures) Regulations* requires FBOs to establish food recall

plans and sets out requirements on how to carry out a food recall through efficient, rapid identification and removal of hazardous food from distribution (Regulation 11). The Regulation also contains provisions for informing consumers. In the CXC 1-1969 and CXG 60-2006, the CAC defines traceability as the ability to follow the movement of a food through specified stage(s) of production, processing and distribution. Legislation should make clear what items fall under the traceability system (e.g. ingredients, raw material and primary packaging materials). The Antigua and Barbuda *Food Safety Act (2020)* requires the establishment of a system that can traceback through all stages of processing to the supplier of ingredients, raw material and primary packaging materials, including transportation, storage and distribution.

Legislation often obligates FBOs to keep records relating to the procurement/supply or sale/recipient (other than to consumers) of a food or ingredient at least one-step forward and one-step back. As previously mentioned in Section 7.2.1, this means that feed manufacturers as well as the owners of food-producing animals fall under the obligation to keep records relating to safety and hygiene. To that end, the *Food Safety Act (2020)* of Antigua and Barbuda requires FBOs to establish and maintain records as prescribed, identifying both the immediate previous source and immediate subsequent recipient of a food (Section 19). Labelling requirements for lot identification or other strategies that identify the producer are important for traceability, but often vary from country to country. In keeping with the *General Standard for the Labelling of Prepackaged Foods (CXS 1-1985)*, at minimum, the law should require a food label to provide clear information about the identity of the product, the list of ingredients used, the name and address of the manufacturer, etc., in a language that can be easily understood by the local population. Point of sale signs and labels may be used for stalls, markets and other informal establishments. Legislation may also impose a traceability number for foods of animal origin (in order to trace the product back to the animal on the farm).

FAO and WHO define "recall" as an action to remove food at any stage of the food chain, including that possessed by consumers (FAO and WHO, 2019). Unsafe food should be prevented from entering the market or should be withdrawn and dealt with appropriately, as recommended in Codex CXG 82-2013. While the primary responsibility for initiating and carrying out recalls rests with the FBO, the law may also empower the competent authority to carry out the recall at the cost of the FBO where the FBO does not comply. Legislation may prescribe the required documentation and reporting procedures for recall actions. Legislation may also require public warnings to be issued as part of the competent authority's risk communication functions (CXG 82-2013).

Legislation should also require that FBOs make provisions for "removed or returned products to be held under secure conditions until they are destroyed, used for purposes other than human consumption, determined to be safe for human consumption, or reprocessed in a manner to reduce the hazard to acceptable levels, where permitted by the competent authority" (CXC 1-1969, p. 21). Such provisions could later be used to ensure that foods that have AMR risks are appropriately dealt with and not disposed into the environment or repurposed without the risks reduced or eliminated.

As noted in the Codex *Principles and Guidelines for the Exchange of Information in Food Safety Emergency Situations (CXG 19-1995)* and the CXG 82-2013, the competent authority could be mandated to develop a surveillance programme and an early warning system or rapid alert system to identify food-borne emergencies, adopt risk-based food safety measures to address the emergency, and to facilitate the exchange of information/. To this end, the Serbian *Food Safety Law (2019)* established a rapid notification and alarm system as a network for reporting direct or indirect risks to health caused by food or animal feed (Article 38). In the European Union, Article 50 of *Regulation 178/2002* established the Rapid Alert System for Food and Feed (RASFF) to enable the exchange of information between member countries and thereby ensure swift response by national food safety authorities. Legislation should establish in broad terms what circumstances would trigger emergency procedures. Often, an emergency response plan is required to be developed that would enable the competent authority to mount an effective and rapid response. In some

jurisdictions, the minimum requirements for the emergency plan, such as procedures and provisions for coordination and communication, are set out in legislation, while the plan itself is not necessarily issued as a legal instrument. As an example, the *Food Safety Act (2020)* of Antigua and Barbuda requires the development of a food safety emergency response plan by the Food Safety Services, in collaboration with other relevant governmental entities, national non-governmental entities and regional authorities. Such a plan must include the creation of a multi-sectoral and multi-disciplinary response team specific to the nature of the emergency (Section 28).

8.1.8. Inspections, laboratories and surveillance

Overview of key regulatory elements of laboratories and surveillance relevant for addressing antimicrobial resistance

- Legislation may establish a national system for surveillance of foodborne diseases.
- Legislation may provide a foundation for food safety monitoring and surveillance systems through provisions on:
  - inspections, sampling and testing;
  - designating official and reference laboratories;
  - exchanging data with national antimicrobial resistance surveillance mechanisms.

Rationale

Inspection schemes (supported by a system of laboratories), comprise the sampling and testing of samples collected during inspections. As the backbone of evidence-based decision-making, international recommendations on AMR strategies give much emphasis to establishing effective AMR monitoring and surveillance systems. Existing food safety surveillance systems can channel country-specific data on AMR risks from food to broader national-level AMR surveillance mechanisms which can also be integrated and aligned with other national surveillance schemes for human health, animal health and the environment. In the context of AMR, laboratories may share surveillance data with other official, reference, and authorized laboratories or other entities undertaking AMR surveillance.

Requirements

In addition to setting out an inspection scheme which grants the power of the competent authority or relevant authority to enter premises, carry out inspections and take samples at all stages of the food chain, legislation may require the completion of inspection reports and records, which may form valuable data on food safety incidents and the prevalence of any AMR-related food safety risks. As an example, Nauru's *Food Safety Act (No. 4 of 2005*), obliges a food inspector to issue a written report that identifies any violation of the law to the owner or the person in charge of the food establishment under inspection, and to lodge a copy of the same report with the Health Inspector and the Director of Public Health (Section 21). Legislation should require the testing of official samples to be undertaken at official laboratories, and the competent authorities should also have the power to designate reference laboratories and those used for quality control. Previous sections have referenced the duty of record-keeping and reporting by FBOs. In order to have effective data exchange and to enable the sharing of laboratory surveillance data across various types of surveillance networks and across different ministries (e.g. those responsible for human health, agriculture and animal health, environment, water etc.), an appropriate legal framework is needed. Legislation should consider data-sharing rules among authorities and for public warnings, and also the protection of sensitive personal and business data.

8.2. Environmental dimensions of antimicrobial resistance

8.2.1. Antimicrobial resistance and the environment: background

There is growing evidence that the environment plays a key role in the development, transmission and spread of AMR (UNEP, 2023). Environmental dimensions of AMR arise through the emissions of antimicrobials (and their residues and metabolites) as well as through the release of antimicrobial-resistant microorganisms and mobility of antimicrobial-resistant genes (Larsson and Flach, 2021). AMR and the environment is a complex subject, characterized by dynamic interactions, cyclic interrelationships, and multiple causalities in a manner that ultimately impacts global planetary health (UNEP, 2023). For example, there is growing evidence of how different types of substances may amplify the development of AMR in the environment, for example herbicides and microplastics (via different mechanisms), biocides, antifouling paint, etc. (Liao *et al*., 2021; Kurenbach *et al*., 2015; Liu *et al*., 2021). Despite interlinked transmission risks, some researchers posit that environmental emissions (of resistant microorganisms) and environmental exposure to the same are nonetheless distinct (Larsson and Flach, 2021).

There are a number of sources and pathways through which humans are exposed to AMR, which all contribute to the development and spread of AMR in the environment. These various sources are collectively referred to in this Study as AMR-relevant pollutants. Pollution is one of the triple interlinked planetary crises (alongside climate change and biodiversity loss) and a country's legal architecture for environmental governance has been identified by UNEP as essential to confront this challenge (UNEP and United Nations Environment Assembly, 2021). Thus, legal frameworks that prevent and manage pollution by addressing sources, sinks and waste will be critical to environmental sustainability on a planetary level.

Natural resources should be suitable and safe for farming (including crop, aquaculture and livestock production). Similarly, water for drinking and for domestic use must be safe for human consumption.

Environmental media can spread antimicrobial-resistant microorganisms within and between humans, animals and the environment. Human exposure to AMR from the environment can take place following consumption of food or water that has become contaminated with antimicrobials or resistant microorganisms (UNEP, 2023). FAO, the WHO and the WOAH emphasize that the three principal means of environmental transmission include: (i) the transmission of disease-causing pathogens which increase the need for treatment with antimicrobials; (ii) transmission of non-pathogenic microorganisms that become evident upon transfer of genes to pathogens; and (iii) antimicrobial residues from use in humans and animals, from disposal and from manufacturing wastes (FAO, OIE and WHO, 2020).

It should be emphasized at the outset that the complexity of these ecological interactions, and indeed the environmental aspects more broadly are undergoing continued research which may shift the current understanding of the environmental dimensions of AMR, and indeed perhaps environmental *impacts* of AMR. More specifically, a "non-strictly anthropocentric" view of the environmental aspects of AMR includes the impact of antimicrobials on the environment *per se*, in addition to the ramifications for the development and spread of AMR in the environment that directly affect humans. For example, some studies show that antimicrobials have toxic effects on ecosystems, reducing microbial biodiversity and inhibiting microbial groups that play a key role in ecosystem functions (ReAct, 2019).

Notwithstanding the rapidly evolving data in the environmental space, which will no doubt alter and influence the policy and regulatory interventions used to address detrimental impacts, this section outlines

key regulatory mechanisms already present in legislation that can be used to mitigate or address the environmental aspects *as they are currently understood*.

8.2.2. Sources and pathways for antimicrobial resistance-related pollutants to enter the environment

As a starting point, it is useful to capture the various ways that antimicrobials (and their residues and metabolites) as well as antimicrobial-resistant microorganisms and genes (hereafter collectively referred to as AMR-related pollutants) enter, develop and spread through the environment. The key sectors contributing to environmental dimensions of AMR can be broadly classified as: (i) manufacturing of pharmaceuticals (human medicines, VMPs, pesticides, etc.); (ii) agricultural production and (iii) healthcare facilities and laboratories (UNEP, 2023). Below, the first two categories are examined in detail, while the latter category falls outside the overall scope of this Study. Other contributors to the environmental dimensions of AMR include poor sanitation, untreated sewage, and community and municipal wastes (UNEP, 2023). The UNEP (2022) and the WHO (2014) have emphasized that human waste is a significant contributor to the transmission and spread of antimicrobial-resistant microorganisms and genes to the environment, through wastewater and sanitation systems.

Within the categories identified in the foregoing paragraph, specific examples of the sources and pathways include: (i) waste from pharmaceutical manufacturing facilities, including antimicrobials for both veterinary and human use, as well as their active pharmaceutical ingredients (APIs); (ii) waste from veterinary clinics and (public health) hospitals; (iii) waste from livestock and aquaculture facilities, including farms, slaughterhouses or other animal/veterinary facilities, as well as manure run-off; (iv) pesticide run-off from farms, direct application of antimicrobials in aerial spraying on crops, as well as inappropriate disposal of pesticide wastes (obsolete or unused pesticides and pesticide containers); (v) human faecal waste from humans treated with antimicrobials, and sewage and water treatment systems; (vi) disposal of unused antimicrobials into the environment; and (vii) direct use of antimicrobials in the environment, e.g. for wastewater disinfection, antifouling.

The foregoing sources and pathways can be separated into "point-source" (discrete, arising from an identified single point, such as those from industries, hospitals, intensive livestock production facilities) and "non-point source" (diffuse, without a single point of origin, such as manure/soil runoff, infiltration from multiple sources that are not readily distinguishable). Facilities manufacturing VMPs and pesticides, for example, would typically be classed as point-source polluting activities. Most agriculture activities comprise non-point pollution sources, with some exceptions. Wastes from concentrated animal feeding operations including piggery and inland aquaculture in closed tanks are however considered point-source pollution (FAO, OIE and WHO, 2020).

For AMR purposes, there is a particular focus on water and soil as receiving environmental media. Good water quality is crucial for human health and for well-functioning aquatic and other ecosystems, while soil ecosystems deliver important services such as the provision of food, energy and raw materials, water purification, nutrient regulation, pest control and support for biodiversity. Food and agriculture sectors both generate AMR-related pollutants and are also also detrimentally impacted by such pollutants. The presence of AMR-related pollutants may negatively affect water resources that are used for drinking, as an agricultural input (drinking water for animals, irrigation for crops, aquaculture), and other anthropogenic activities. There is a direct link between water quality used for irrigation and resistant-bacteria on food, particularly on fresh fruits and vegetables (FAO and WHO, 2019). It is estimated that approximately 70-80 percent of antibiotics used in aquaculture are excreted into water and disperse into the environment through water systems (Serrano, 2005; Burridge *et al*., 2010). AMR may have detrimental effects on the functional, structural

and genetic diversity of soil microbial communities resulting in reduced soil functionality (Cycon, Mrozik and Piotrowska-Seget, 2019). The persistence of antimicrobial-resistant microorganisms and genes in the soil environment depends on a range of environmental and climate conditions and factors (FAO, 2021a).

Legal frameworks to prevent and control pollution provide various mechanisms, which will be explored in the sections below, that can be used to address the release of AMR-related pollutants into the environment, and to address environmental transmission of resistant microorganisms.

8.2.3. Where can regulatory tools impacting the environment be found?

Legal frameworks for mechanisms to prevent and control the spread of AMR-related pollutants can be governed by a range of laws, including legislation governing specific environmental media – such as water management legislation or soil legislation – as well as their corresponding quality standards; general environment-related legislation; pollution prevention and control legislation; chemicals management legislation; legislation on natural resources, including laws on biodiversity, climate change, wildlife and forestry; protected areas legislation; agriculture legislation for all types of production systems; water infrastructure, sewage, sanitation and wastewater legislation; pharmaceuticals legislation; procurement legislation; business authorization legislation; and waste management and disposal legislation.

Relevant provisions for waste management can be found in general waste management legislation, municipality legislation or landfill legislation. Waste laws may be established for waste in general, or specifically for medical waste. Waste management may also be addressed in legislation on the environment, business authorization, soil, noxious or polluting activities, agriculture, health, pharmaceuticals, pesticides and feed. Finally, there could also be relevant elements in legislation on sustainability, circular economy, recycling and waste reduction.

8.2.4. Institutional frameworks: a focus on coordination and collaboration

Overview of coordination mechanisms in institutional frameworks for environmental management

- Legislative provisions for cooperation or coordination among the environmental agency and the authorities responsible for human health, (terrestrial and aquatic) animal health, and agriculture can be used to address multidisciplinary aspects of of antimicrobial resistance (AMR) and the environment.
- Where environmental management responsibilities are shared between centralized and decentralized (local/provincial level) institutions, mechanisms for coordination that integrate these levels are important.
- A duty by the line ministry to consult the environmental authority on sectoral decisions affecting the environment provides an entry point for engagement on AMR matters.
- Legislative provisions for stakeholder participation or consultation in natural resource management brings together of stakeholders relevant to AMR and the exchange of information.

Rationale

A legal underpinning of clearly delineated roles and functions of various private and public actors impacts the effectiveness of environmental management; moreso for a multisectoral challenge such as AMR which should bring together a range of actors and industries at the human-animal-environment interface.

Mandates for environmental management and the need for coordination

In most jurisdictions, environmental management processes sit within the competence of an authority designated to protect the environment (whether this is a ministry, statutory body or a department within a ministry). Regardless of the arrangements, institutional coordination between such body and the agencies responsible for agriculture and public health, among others, is essential in order to adequately address the environmental dimensions of AMR. The institutional arrangements set out in environmental legislation vary widely per jurisdiction (as do the mechanisms for coordination and collaboration), and indeed there is variance within a jurisdiction on the institutional arrangements to regulate different types of natural resources.

Environmental legislation, sectoral legislation or even the national constitution may establish the functions of the various levels of government, delineate roles and responsibilities, and establish powers within the various departments. Legal provisions should be made for effective institutional coordination (involving "vertical" cooperation at various levels of government as well as intersectoral "horizontal" coordination).

Duty to consult environmental authority or comply with environmental legislation

Various mechanisms exist which push authorities to include environmental considerations in decision-making. Sectoral and environmental legislation may make a general reference to the observance of the country's environmental norms in undertaking various types of industrial or agricultural activities. Furthermore, sectoral legislation governing the manufacturing of VMPs (including APIs) or on agricultural production (crops, livestock, aquaculture) – in addition to environmental laws – may also include the obligation to consult with the environmental authority before certain actions or management decisions can be taken by line ministries. This is different to the issuance of a permit to a private actor that requires environmental approval (see section 8.2.8 of this Study). Rather, this refers to the duty of line ministries to consult environmental authorities, for example, during the development of master plans for the aquaculture sector, or for the creation of manufacturing zones. Land zoning ensures appropriate siting of various operations to minimize the potential impacts of the activity (including waste discharge). The siting of facilities and installations may require by law a consideration of the socio-economic impacts and other impacts on local communities, e.g. impacts on public health.

Tools for coordination and stakeholder consultation

Effective stakeholder engagement provides important local AMR-related knowledge, buy-in for any AMR-specific initiatives and compliance with resource management measures. Legislative provisions that establish any type of mechanism for joint implementation activities across multiple sectors are particularly useful. Collaboration may take many forms from formal agreements relating to responsibilities in areas of common authority to joint work plans. Memoranda of Understanding (MoUs) or service-level agreements may be advocated by legislation to cement cooperation arrangements. In South Africa, the *National Environmental Management Act (1998)* requires the creation of environmental management plans that include a description of arrangements for cooperation between the different national departments and spheres of government, including any existing or proposed MoUs entered into, or delegation or assignment of powers to other organs of state, with a bearing on environmental management (Article 14)

Advisory or stakeholder bodies may be established for (depending on their composition) designing, implementing, advising on, or monitoring environmental management measures. Executive decision-making bodies comprised of government agencies only (including those for public health, industry and agriculture), or broader multistakeholder advisory or consultation bodies (that include the private sector) are useful fora to address intersectoral and multidisciplinary issues such as AMR. In Tanzania, *the Environmental Management Act (No. 20 of 2004)* establishes the National Environmental Advisory Committee as the advisory body to the minister responsible for the environment (Article 11). This Committee, which is composed of members from the public and private sectors and civil society (Article 11), advises the minister for the environment or any sector ministry on any matter which may be referred to it, and in particular, is responsible for reviewing and advising on any environmental standards, guidelines and regulations (Article 12).

Stakeholder participation enabled through provisions on access to environmental information held by public authorities (e.g. EIAs), or through advisory bodies, can ensure that multiple perspectives (AMR-related, and other) are taken into account in environmental decision-making. In Lesotho, the *Environment Act (No. 10 of 2008)* has a specific provision on freedom of access to environmental information, which covers data relating to the implementation of the Act as well as other information concerning the management of the environment or natural resources (Article 95).

8.2.5. Regulatory responsibilities: a focus on standard-setting, enforcement and monitoring

Overview of responsibilities for standard-setting, enforcement and monitoring

- Legislation should designate the entity(ies) responsible for setting standards and targets (and the process for doing so) and the entity(ies) responsible for enforcement, including inspections and monitoring.
- Key responsibilities of environmental authorities (at centralized and decentralized levels) include monitoring and surveillance of resources such as water, incorporating data collection, data analysis and data exchange/communication.
- Environmental quality standards for water and soil may be used to include AMR-specific parameters (subject to available resources and technical feasibility for implementation in practice).
- Regulatory control mechanisms must set out a system of assessing the water condition, identifying point sources and determining the standards needed to achieve desired water quality standards relative to the uses of the water.

Rationale

Among the myriad functions allocated to environmental agencies, this section focuses on standard-setting, enforcement and monitoring responsibilities related to the protection of soil and water resources as the latter are the principal receiving media for AMR-related pollutants.

Standard-setting and enforcement for soil and water

Legislation should establish or designate the entity responsible for setting standards and targets (and the process for doing so) and the entity responsible for enforcement, including inspections, and monitoring. These regulatory roles may be allocated to different government entities (either 'vertically' at different levels or 'horizontally' across different agencies).

Legislation on water and soil is commonly separated. While some of the regulatory mechanisms are similar for soil and water (pollution control, treatment, standard-setting and enforcement, etc.), there are distinct technical considerations related to the different media, and specific technical standards are issued by the relevant (sometimes different) competent authority. The objectives of these laws and standards are to ensure that the quality of the resource is safe for the intended purpose and function. Furthermore, there is a technical connection between these two resources, and this soil–water nexus is recognized in some soil and water laws, through provisions that address water source contamination by surface runoff, and by build-up and leaching of pollutants. Both soil and water laws include general clauses requiring the protection of the resource against pollution. Water quality and soil quality standards, coupled with provisions on sampling and testing, offer frameworks into which AMR-specific parameters may be subsumed. Technical details, such as numerical quantities (for example of antimicrobial pollutants) are typically relegated to lower-level legislation or Schedules or Annexes, depending on the jurisdiction.

Water quality standards are classified in accordance with the end use of that type of water, i.e. for irrigation, agriculture, aquaculture, drinking and sanitation, etc. or are used to classify water bodies into different categories, which are used for planning. These standards ensure water quality is sufficient for such designated uses by establishing the maximum permissible contaminant concentration that permits the standards to be met under all likely conditions (FAO, 2009). Water quality standards that take into account maximum thresholds for different types of antimicrobials may possibly be introduced under such provisions. Tanzania's *Fisheries Regulations (No 308 of 2009)* requires that aquaculture facilities are required to have water samples from their establishments analysed in an official laboratory in accordance with their sampling plans (Regulation 111). In addition, the competent authority should carry out verification sampling and testing which includes parameters relating to antimicrobial residues and veterinary drugs (Regulation 111). Sao Tome and Principe's *Water Resources Framework Law (2018)* establishes monitoring and surveillance with regard to quality aspects, i.e. a focus on water intended for human consumption and domestic uses, irrigation water, and wastewater, including of agricultural origin (Article 50). Brazil's *CONAMA Resolution 357/05* sets out a range of considerations for assessing water quality conditions and setting water quality standards. The water quality class is defined as "the group of conditions and standards necessary for current or future preponderant usage." Although the text indicates that the Resolution will establish individual limits for each substance to be monitored by the competent authority, there is room for including additional parameters at various junctures in the text, particularly in Chapter III, as follows: the quality of aquatic environments may be assessed through biological indicators and through the use of aquatic organisms; the presence of contaminants not listed in the Resolution may be investigated via certain tests and methods; and the competent authority is empowered to add other conditions or water quality standards based on scientific justification. The European Union adopted *Directive 2008/105/EC on environmental quality standards in the field of water policy*, which sets water quality standards for surface waters. A recent implementing decision from the Commission under *Decision (EU) 2018/840* included amoxicillin and ciprofloxacin to the watch list of hazardous substances related to water quality standards, and explicitly acknowledged that their addition to the list is consistent with *A European One Health Action Plan against Antimicrobial Resistance*.

Safe quality targets apply not only to recipient waters but to the wastewater which contains complex microbial communities. Regulatory control mechanisms must set out a system of assessing the water condition, identifying point sources and determining the effluent standards needed to achieve desired water quality standards relative to the uses of the water (FAO, 2009). In Uganda, under the *National Environment (Standards for Discharge of Effluent Into Water or Land) Regulations (2020)*, a person is forbidden from discharging effluent into either water or land, except in accordance with the relevant environmental laws and environmental standards (Article 5). These Regulations also establish the environmental standards for effluent for general chemicals and microbiological discharge (Article 6). Establishing effluent standards requires first that measures for attaining such standards are both technically feasible and essential to

achieving the objectives for the receiving water (FAO, 2009). The relevant wording in the law may often be sufficiently broad to include AMR-related data once the appropriate parameters have been decided (e.g. possibly using resistant pathogens as indicators for AMR versus the presence of certain chemicals as indicators).

With regard to the intersection of water, sanitation and hygiene (WASH) matters – and specifically the AMR risks from wastewater containing excreta – the WHO (2015) has established key functions for regulatory authorities which require coordination of agriculture, health and environment considerations: (i) establishing targets and standards based on the tolerable risk to human, animal, and environmental health; (ii) risk assessment and management within sectors (this may include identification of priority risks within sectors, the means for risk mitigation, as well as controls around the various sources of pollution); and (iii) reporting and monitoring.

The Stockholm Framework for the development of water-related guidelines and the setting of health-based targets is an integrated approach that combines risk assessment and risk management to control water-related diseases (WHO, 2006). Regulators should establish health-based targets that define the level of health protection for a given exposure. Once the level of health protection is defined, a combination of health protection measures that could achieve the target are specified across the production/consumption continuum. According to WHO guidelines, legislation should set out which entity is responsible for: identification of hazards; generating evidence for health risks and effectiveness of possible health protection measures to address them; health-based targets to manage health risks; implementing health protection measures to achieve the health-based targets; and system assessment and monitoring (WHO, 2006).

In Sweden, under the *Environmental Code (1998 as amended in 2008),* wastewater discharge is considered as an "environmentally hazardous activity" (Chapter 9, Section 2), and as such is subject to permit and notification requirements. The Code also requires that wastewater is to be diverted and treated in order to avoid risks to human health or the environment by using appropriate sewerage systems or other works. The Environmental Code further allows the government to issue rules related to the quality of water where this is necessary in order to provide lasting protection for (and remedy adverse effects on) human health or the environment. Environmental quality standards specify the levels of pollution to which the general public or the environment may be exposed without any risk of significant detriment. The standards indicate the maximum or minimum occurrence in surface water and groundwater of chemical products or biotechnical organisms; as well as the maximum or minimum level or value relating to the water level or the flow in water systems, watercourses, groundwater or parts thereof (Chapter 5, Section 2).

In relation to receiving waters, the sensitivity of groundwater to pollution, and its status as a primary source of drinking water (often with little to no treatment) for some communities, means that the discharge of wastewater into wells and other groundwater sources is either prohibited outright or subject to strict controls, such as a specialized permit and prescribed treatment specifications. Where groundwaters are already contaminated, remedial treatment is a complicated, lengthy and expensive process – and in such areas prevention of pollution is a policy imperative.

The competent authority for water management (often at local or municipal level) may also be responsible for monitoring water quality, and powers are often included in legislation to take samples. In the United States, the *Federal Water Pollution Control Act (Clean Water Act)* of 1972 created the National Pollutant Discharge Eliminated System, which regulates point sources that discharge pollutants into water bodies. For cases where the contaminant does not have a regulatory standard, as may be the case for some substances contributing to AMR, the Unregulated Contaminant Monitoring Rule may provide an avenue to control pollution of drinking water. The Environmental Protection Agency can use the Rule to monitor 30 agreed chemicals for a five-year cycle to understand the frequency and level of occurrence of unregulated contaminants in the nation's public water systems (US-EPA, 2021).

Soil or land legislation may govern the substances used in agriculture or otherwise released into the soil. Legislation should establish pollution parameters and the specific pollutants that will be subject to periodic monitoring. Agriculture laws or environmental laws may also govern soil quality through provisions for monitoring residues in soil or by prohibiting soil contamination. Owing to their technical nature, soil quality standards are often set out in administrative instruments or standards. Soil standards may prescribe the permitted concentrations of substances (e.g. antimicrobial residues), which may vary according to land type and use (e.g. agricultural, industrial, etc). Soil standards typically set out methodologies and procedures for assessing soil quality or contamination and for carrying out risk assessments in relation to land use and any remediation measures. Soil quality is often monitored through plans and targets. In some cases, landowners are required to prepare plans for soil management that outline specific soil conservation measures. Legislation may require landowners to investigate, assess or remedy pollution or contamination; alternatively, this may be a specific function assigned to the competent authority.

Responsibilities for monitoring and surveillance

Monitoring and surveillance is a pillar of AMR strategies at international, regional and national levels. Monitoring and surveillance provisions are also core to environmental management, and consequently, important for the collection of data on environmental dimensions of AMR.

Periodic monitoring of environmental media is necessary to determine compliance and enforcement actions, including required environmental remediation and other measures to be taken. Monitoring schemes at different tiers (local, regional or national) require technical and financial resources from the government. However, some of these costs can be offset in the countries where industries are given the responsibility to monitor and report, while authorities are responsible for oversight and aggregating the different data. If the competent authority in charge of water for irrigation has the power to monitor water used in agriculture, such authority may additionally verify maximum limits of antimicrobials and as well as the microbial content of the water.

Coordination is also important for effective environmental monitoring and surveillance as data is collected, analysed, exchanged and used by different entities at local and central levels. North Macedonia's *Law on Environment (2005)* requires the environmental authority to carry out monitoring through "systematic observation, investigation and assessment of the pollution and state of environmental media and areas as a whole, and identification and registration of the sources of pollution of individual environmental media and areas" (Article 32). The national level entity is assisted by state monitoring networks (Article 33) as well as local monitoring networks (Article 34). Monitoring efforts are further supported by a provision requiring businesses that are responsible for sources of emissions to carry out internal monitoring (Article 36). All the data is managed and coordinated through an environmental information system (Article 40).

Even in highly centralized jurisdictions, local authorities typically carry out inspections and environmental monitoring. From an AMR perspective, monitoring and surveillance of water or soil quality using AMR-relevant parameters requires collection of data at sectoral (local) level and analysis at national level, compiled from different sectors. Environmental legislation provisions on surveillance typically assign functions covering data collection (sampling, testing, reporting), data analysis, data exchange among authorities and data communication to the public. In Liberia, this task is given to the Environmental Protection Agency in Article 34 of the *Environment Protection and Management Law (2002)*, which requires the Agency, in collaboration with other relevant ministries and agencies, to establish a monitoring system that provides regular reports on polluting facilities, industries and activities in Liberia. North Macedonia's *Law on Environment (2005)* requires a specific methodology to be followed for environmental monitoring and establishes an obligation for those responsible to submit monitoring data to the national environmental authority. For the purpose of assessing the risk to human health and the adverse impacts on the environment,

the national environmental authority is to periodically submit the monitoring results to the health authority at state level (Article 37).

The legal foundation for these environmental monitoring systems can be used to include AMR-relevant data that is subsequently funneled towards national-level AMR surveillance mechanisms. In some jurisdictions data exchange among institutions or use of data for multiple purposes must be specifically prescribed; in such cases, related practical expansions can be made, for example wastewater surveillance for COVID-19 infection may be expanded to include AMR parameters. Furthermore, existing surveillance programmes for *E. coli* and faecal coliforms which are widely applied in many countries may be used to assess risks for environmental transmission of resistant microorganisms (i.e. both release of and exposure to such microorganisms).

It is recognized that, presently, the methodologies and technologies for collecting certain types of data may not be technically or financially feasible, making this option feasible from a legal perspective in some countries but perhaps impractical from a technical perspective in many countries. However, legislation may distinguish data collection for routine use (such as from inspections programmes) from data that is required for research or investigative studies (which may be more costly and technically challenging). Data collection from inspections activities is used to ascertain compliance with legislation and may result in enforcement actions (remedial measures or financial penalties). Decision-makers can also use the collected data to determine which risks should be prioritized and to determine appropriate regulatory interventions, thereby closing the regulatory feedback loop. Where the surveillance system is well coordinated, the data may result in a shift in regulatory emphasis towards, for example, incentivizing certain industry practices, or a change in the locus of regulatory interventions.

8.2.6. Scope of pollution and waste legislation

Overview of the scope of pollution laws and waste laws

- Definition of terms such as 'pollutant' or 'waste' determine the scope of regulatory action
- Legislation may define pollution or a pollutant in such a manner as may include AMR-relevant pollutants
- Pollutants and wastes can be divided into different categories that may trigger the application of diverse regulatory mechanisms

Rationale

The definition of key terms employed in a legislation determine the scope of regulatory actions and mechanisms that can be applied.

Definition of "pollutant"

Environmental laws often establish a definition of pollution (and such definition is typically broad in scope). Legislation may also define or establish a mechanism to identify the substances that are considered pollutants. A third way is for laws to list the substance or substance categories classified as pollutants. The flexibility of how pollutants are defined may allow for inclusion of AMR-relevant biological and chemical pollutants to be brought within the scope of the legislation and thus subject to regulatory controls. An example of blanket provisions prohibiting pollution, that provide a legislative "hook" under which to introduce AMR-relevant pollutants, can be found in the Finnish *Environmental Protection Act (2014 as*

amended in 2019), which defines "environmental pollution" as: "such emissions that either alone or together with other emissions: a) cause harm to health; b) are detrimental to nature and how it functions; c) prevent or materially hinder the use of natural resources; d) cause a loss of general amenity of the environment or of special cultural values; e) reduce the suitability of the environment for general recreational use; f) cause damage or harm to property or impairment of use; or g) constitute a comparable violation of the public or private interest;" (Section 5). The same Act defines "emission" as: "the direct or indirect release, discharge or deposit of substances, energy, noise, vibration, radiation, light, heat or odour caused by human activity from point or diffuse sources into air, water or onto land" (Section 5).

Some jurisdictions identify the activities or facilities that may generate "pollution" or "noxious" substances. It is therefore important to determine whether the activities canvassed in section 8.2.2 of this Study would be covered by the law. Often agricultural and manufacturing facilities are specifically identified.

Definition and categories of "waste"

Waste legislation often contains definitions that delineate the scope of waste types/categories and thus, a first step would be to see if antimicrobials (including metabolites), antimicrobial-resistant mircoorganisms or antimicrobial residues would fall under any of the categories/definitions. This would determine which regulatory regime would apply to the AMR-related pollutant (if any). There is considerable variation in how countries categorize their waste. These categories of waste are then subject to specialized rules and requirements. Commonly, different requirements (and corresponding emission standards) are established for various types/classifications of waste based on: (i) the associated risks (e.g. a distinct framework for hazardous waste); or (ii) the source of the waste (agricultural, industrial, household, etc.). For example, Saint Lucia's *Waste Management Act (No. 18 of 2004)* defines biomedical waste as "any waste that includes any solid waste containing human or animal fluids, flesh, bones or other body parts except hair" while hazardous waste is defined according to a list included in the Schedule. Schedules to the Act contain detailed design and operating standards for facilities that treat and manage various types of waste.

8.2.7. General mechanisms to address pollution

Overview of common legislative mechanisms to address pollution

- National pollutant release and transfer registers may be used to track/trace AMR-relevant pollutants.
- Legislative provisions that establish financial or other incentives for manufacturing technologies and procurement rules that favour products produced in compliance with prescribed environmental standards may contribute to reduced AMR-related pollution.
- Legislative provisions on the "polluter pays" mechanism and environmental remediation may offer avenues of redress for AMR-related pollution.

Rationale

Environmental legislation offers a range of mechanisms to prevent and control pollution that can be employed to address AMR-related pollutants. Some common mechanisms of particular relevance to environmental dimensions of AMR are canvassed below.

Pollutant registers

Pollutant release and transfer registers are publicly accessible databases of chemicals or other pollutants that are released to environmental media and transferred off-site for treatment. Legislation can create a duty for the competent authority to establish and maintain such registers. In principle, such registers may be used to track AMR-relevant data. Jamaica's *Natural Resources Conservation (Wastewater and Sludge) Regulations (S.I. No. 69A of 2013*) requires the competent authority to maintain a pollutant release and transfer register which registers the quality of effluent being discharged and the status of compliance for treatment plants licensed to discharge effluent (Regulation 46).

Financial and other incentives

Financial tools, such as economic incentives for the adoption of cleaner technologies and improved facilities/infrastructures, are also effective at reducing point-source pollution. Legislation may establish these tools in the form of incentives (such as tax abatements, green bonds and subsidies) or disincentives (such as taxes on the use of specific materials in processing). In Kenya, the *Sustainable Waste Management Act (No. 31 of 2022*), grants the competent authority the power to introduce incentives for locally produced and imported sustainable waste management equipment and materials (Section 25). Legislative provisions on procurement of antimicrobials as well as provisions governing state subsidies of antimicrobials, may prioritize products that have been manufactured in accordance with required environmental standards and priorities, particularly regarding release and management of waste from production facilities.

Polluter pays and remediation

Many environmental laws contain the "polluter pays" principle, which posits that the entity responsible for generating the pollution to bear the costs of managing it, in order to prevent damage to human health and the environment. This principle is most commonly applied to manufacturing- and industrial-sourced pollution, and would for the purposes of this Study likely apply to the discharge of antimicrobials only. North Macedonia explicitly mentions this principle in Article 9 of the *Law on Environment (2005),* which states that the polluter shall compensate the costs to eliminate the danger of the environmental pollution, bear the remedial costs and pay a fair compensation for the damage caused to the environment, and thus restore the environment to the pre-pollution condition to the extent possible.

Inherent in this principle is the identification of an entity that can be held responsible for certain emissions into the environment. Where numerous actors are responsible, laws may establish joint or several liability for remediation or clean-up costs for environmental pollution. Legal responsibilities may include financial penalties for the cost of clean-up or remediation, or the carrying out of remediation measures. Legislation may impose strict liability for environmental damage, meaning proof of negligence or deliberate offences do not need to be demonstrated to hold the responsible party liable for clean-up costs. However, an identification of responsible parties may be difficult, as may be measuring the ecological damage which must be compensated.

Legislation may contain various specific technical recommendations concerning remediation and restoration measures to be taken when an environmental media is polluted (like soil or water). Alternatively, legislation may contain a general clause requiring the taking of such measures needed to address the harm caused. Eswatini's *Environmental Management Act (no. 5 of 2002)* declares that a person who discharges a contaminant likely to cause an adverse effect on the environment shall immediately notify the competent authority as well as take all practicable steps to contain the discharge and to avoid, mitigate and remedy the adverse effects (Section 35).

8.2.8. Preventing and controlling pollution through licences and other operator obligations

Overview of operator licensing and other obligations pertaining to the environment

- Legislation may require licensing for certain facilities that involve the manufacture or large-scale use of antimicrobials (manufacturing, laboratories, farms, hospitals, etc.) which offer a means to control pollution emitted from these facilities.
- An environmental impact assessment may be required as part of an application for a license to operate.
- As a condition of their license, licensees may be required to:
  - submit to periodic inspections;
  - self-audit for environmental compliance;
  - report on prescribed data;
  - develop plans for waste management as well as emergencies

Rationale for using requirements and conditions embedded in licences to operate

Section 8.2.2 of this Study outlined the activities that contribute to AMR-related pollutants. A key mechanism to regulate these activities is through permits or licenses to operate. Various requirements (during the application stage) and conditions (during the operations stage) for a licence to operate may involve requirements that can be used to introduce AMR-related considerations.

In some countries, licences are only imposed on large-scale agricultural operations. However, it should be noted that smaller farms may cumulatively contribute to significant AMR-related pollution and therefore, these should be monitored and controlled by the competent authority.

Environmental impact assessments

Legislation may stipulate the need for an EIA to be undertaken and submitted to the competent authority for environmental matters before approval is given for the issuance of a licence by the relevant authority. Most often, EIAs are required for large-scale or commercial farms (e.g. crop, livestock or aquaculture) or to operate a manufacturing facility for antimicrobials and active pharmaceutical ingredients. Such EIAs can be used to prevent, address and minimize pollution from these sources generally. Under Belize's *Environmental Protection Act, 1992 (Cap. 328, as amended in 2011)*, EIAs are required from any person intending to undertake any project, programme or activity which may significantly affect the environment (Section 20). Finland, under the *Decree on Environmental Impact Assessment Procedure (2006)*, mandates an EIA for animal husbandry projects above a certain threshold of animals, as well as for hazardous waste treatment plants above a certain volume of hazardous waste (Section 6). Hazardous waste itself is defined in Finland's *Waste Act (as amended in 2007)* as "any waste with properties that render it flammable or explosive, infectious, or hazardous to human health or the environment in other ways, or with other corresponding properties" (Section 6).

An EIA usually involves a determination of baseline data that takes note of existing environmental conditions (as well as social factors, including public health), followed by an identification of the direct and indirect

impacts on the natural resources and local population. Also included in an EIA is the probability of those impacts, their significance and any mitigating steps that can be taken to reduce harm or to reduce the likelihood of occurrence. An EIA should cover all stages of an activity/facility – from its inception to its cessation, and through all the operations in between. According to the Ethiopian *Environmental Impact Assessment Proclamation (No. 299 of 2002)*, without authorization from the competent authority, no person is permitted to commence any project listed in the Proclamation as requiring an EIA without one (Section 5). The Proclamation states that the impact of a project shall be assessed on the basis of the: size, location, nature, cumulative effect with other concurrent impacts or phenomena, transregional effect, duration, reversibility or irreversibility or other related effects of the project (Section 4). Specifically, EIA reports should include the types and quantities of pollutant that will be released by the project (Section 8). The Proclamation calls for the cooperation of licensing authorities to ensure operating, investment or other trade licences are not issued without an authorization from the relevant regional authority on environmental matters (Section 3). Projects can be approved with conditions to mitigate negative impacts where such externalities can be reduced (Section 9).

An EIA should identify risks and propose options to mitigate risks. An EIA may also require certain restoration measures as a pollution contingency. The requirement of an EIA may be contingent on the size of the proposed activity or the environmental sensitivity of the area. Typically, an EIA should evaluate cumulative effects, and address broader impacts (sometimes referred to as a "cumulative impact assessment", which includes uncertain or irreversible consequences). An EIA may concentrate on environmental elements only or incorporate broader elements as an environmental and social impact assessment (ESIA).

While EIAs may be a requirement of a licence, this process is also used (independently) by competent authorities to determine whether a given area is suitable for the commencement of certain activities, e.g. aquaculture zones, slaughterhouses, etc.

Environmental audits

Legislation may require a commercial activity to undertake environmental audits. The basic objective of such audits (self-assessment or via a third party) is to enable a systematic and periodic scrutiny of operations to ensure environmental requirements are met. The legislation often imposes an explicit duty to monitor environmental compliance in the law and as a condition of a licence. Fiji's *Environment Management Act (No. 1 of 2005),* states that development projects require an EIA (Section 27), and as a part of this authorization process, the proponent must prepare and implement environmental or resource management plans, monitoring programmes, and protection plans or mitigation measures that are required as a condition of any approved EIA (Section 32).

Waste management plans

Legislative provisions requiring an operation to develop a waste management plan as a condition for applying for a licence offer a means to ensure facilities have appropriate mechanisms to reduce the risks of AMR at the planning stage. These types of plans are most commonly associated with manufacturing facilities or large-scale farms. A waste management plan typically details how the proposed operation will reduce waste production, treat waste, and ensure its safe transport and disposal. Legislation often requires such plans, once approved, to be subject to periodic review. Kenya's *Sustainable Waste Management Act (No. 31 of 2022),* requires private sector entities to prepare three-year waste management plans and submit an annual report to the competent authority. In such plans, businesses are required to specify the actual quantities of waste generated, the waste management methods applied, and any other information that the competent authority may require (Section 19).

Legislation may detail minimum aspects of such plans such as monitoring schemes and measures to be taken once there is contamination of a site above a prescribed threshold. Legislation may also require waste management plans to include aspects such as: details on how the proposed plans have been successfully implemented in other jurisdictions; storage and handling of waste, including quality assurance and control; specific responsibilities of those tasked with waste management; and monitoring and reporting.

Reporting

Environmental audit duties are typically accompanied by obligations to submit periodic reports to the environmental authority. For example, in Botswana's *Environmental Impact Assessment Act (No. 10 of 2011)*, the relevant technical department, local authority or developer, is required (during and after implementation of a licensed activity) to monitor the implementation of the activity for compliance with the agreed mitigation measures. The developer is to submit an evaluation report to the relevant technical department or local authority, at such times as the department or local authority requires (Section 18).

These legislative obligations may be expanded to include, for example, the duty to track volumes or concentrations of antimicrobial effluent, and the duty to use specific mechanisms of disposal. Inspections by the competent authority ensure that obligations are met. Licensees may also be obliged to carry out response measures for exceptional circumstances (such as leaks, malfunctions, temporary or permanent stoppages, etc.), which would address, for example, unintended or accidental release of antimicrobials into the environment.

Waste/wastewater discharge permits (see Section 8.2.9 of this Study) may also be conditional on periodic self-auditing and reporting to the competent authority during operations. Such authorizations are required in addition to a licence-to-operate or may form an integral part of such a licence. Record-keeping and reporting measures may involve tracking the movement of waste until its safe treatment or disposal. Malawi's *Water Resources Act (No. 2 of 2013)* allows the competent authority to include requirements in the discharge permit such as monitoring, analysing and reporting on every discharge under the permit (Section 94).

The WHO working document on *Environmental Aspects of Good Manufacturing Practices: Points to consider for Manufacturers and Inspectors in the Prevention of Antimicrobial Resistance* calls for the need to require specific information from the manufacturers (WHO, 2019). This comprises data such as: waste stream analysis for each antimicrobial agent produced; the quantity and nature of the waste generated, including documentation of analysis performed and their findings on the hazardous substances it contains; and information on the methods used to treat the waste.

8.2.9. Targeting activities that generate pollution

Overview of key regulatory mechanisms targeting activities that generate pollution

- Legislation may prohibit the siting or conduct of certain activities (which may include the manufacture or use of antimicrobials) in certain areas.
- Prior to the discharge of waste, legislation may require:
  - authorization, e.g. via issuance of a discharge permit;
  - treatment of waste.
- The legislative framework should require the effective functioning/operation of wastewater treatment plants and related infrastructure.

Rationale

Environmental legislation offers a range of mechanisms used to target activities that generate pollution. Some common mechanisms of particular relevance to environmental dimensions of AMR are canvassed below.

Geographical restrictions and prohibitions

Legislation may expressly prohibit manufacturing, agricultural or other prescribed activities in certain areas (e.g. near water bodies, schools, densely populated areas or protected zones), and a determination should be made whether the activities that are prohibited include those identified in Section 8.2.2 of this Study. For example, environmental or sectoral legislation may restrict sites or locations for aerial spraying of pesticides, or may prohibit the construction of hospitals or livestock farms near water bodies, particularly where such water bodies are sources of drinking water, fishing, irrigation, etc. In Seychelles, the *Environment Protection Act (No. 18 of 2016)* grants the minister responsible for the environment the power to declare a protection zone to protect catchment areas used for abstracting drinking water and to prohibit or regulate activities in the protection zone which may directly or indirectly affect water quality (Article 18).

Antimicrobial contamination from aquaculture establishments is most obvious in open water or in flow-through systems, but it should be recalled that water bodies are comprised of interconnected networks, cycles and processes. Thus, water inputs in agricultural locations where background levels of antimicrobial residues are already high in the water or soil further increases the levels that will be discharged, in addition to the residues in the agricultural products themselves. This places primacy on the need to restrict and control proximity of certain types of agricultural activities to surface or underground water bodies, but also highlights the risk that antimicrobial contamination can flow to sites that are further away. These provisions are largely found in water laws, however, fisheries and aquaculture legislation may also contain relevant provisions. These include preventing water pollution during capture and production, and prohibiting unacceptable levels of pollutants in fishery and aquaculture products. Legislation may restrict the location of aquaculture activities and site them away from environmentally sensitive areas.

Environmental monitoring and inspections track and control impacts at a particular site. Provisions relating to monitoring the discharge of effluent in these areas can be used to introduce AMR-relevant parameters (noting the comments on technical feasibility in Section 8.2.5 of this Study). Legislation may establish provisions for the management and remediation of sites that are contaminated.

Waste and wastewater: permits, treatment, infrastructure and monitoring

Wastewater discharge from agricultural, industrial, household and other sources may contain all types of AMR-related pollutants. Thus, any mechanism that regulates wastewater may offer a suitable vehicle for the introduction of AMR-related parameters and considerations. Many jurisdictions require EIAs prior to granting concessions for wastewater discharge and EIA's can be used to anticipate the effects of (and thereby control) the discharge of wastewater from crop, livestock and aquaculture production. Specific AMR-relevant criteria can be introduced in the treatment and management of sewage sludge and in the reuse of wastewater in agriculture, and these should be subject to the same level of treatment as human wastewater systems (FAO, OIE and WHO, 2020).

Legislation may either completely prohibit the release of waste or wastewater into various environmental media (such as soil or water sources), or may condition release subject to a permit and prior adequate treatment of waste or wastewater. In Saint Lucia, following the requirements in the *Water and Sewerage Act (2005),* the discharge of waste or class of waste in a waste control area is subject to a permit from the minister responsible for water resources (Article 25). In Mauritius, the *Environment Protection (Effluent Discharge Permit) Regulations (2003)* prohibit the discharge of any effluent from selected activities (such

as industrial slaughter plants and livestock breeding operations) into a watercourse, water body or onto land without an effluent discharge permit (Regulation 3).

Legislation may stipulate that discharge permits are required by any facility that carry out waste treatment, whether professionally or as part of the manufacturing of pharmaceuticals. The issuance of discharge permits may be conditional on compliance with effluent standards. Criteria relating to discharge permits, whether as requirements for the issuance of the permit or conditions for maintaining such a permit, may be amended for antimicrobial waste to include AMR-relevant parameters in emission limit values. Authorized discharges are to be monitored and controlled by the competent authority, and in addition, legislation should identify the competent authority responsible for issuing as well as monitoring and enforcing effluent standards. As noted in section 8.2.9 of this Study, discharge authorizations are usually accompanied by obligations of operators to monitor compliance with limits and to submit periodic reports to the competent authorities (primarily through self-monitoring and disclosure).

Legislation that establishes provisions governing WASH infrastructure and the functioning of wastewater treatment plants/infrastructure is also important. Among other aspects, wastewater laws include provisions for: collecting and treating wastewater; rules relating to locations or water bodies available to receive discharge; and rules governing treatment infrastructure (FAO, 2009). In Mauritius, the *Wastewater Management Authority Act (2001*) establishes a competent authority, defines its functions and powers, contains rules relative to its internal organization, and contains some provisions regarding the discharge of effluent or wastewater. Pertinently, this authority is to undertake water treatment to the prescribed quality for the safe disposal of effluent and sludge into the environment or for re-use, as well as to control pollution that is discharged into the wastewater system (Section 5).

Considerations relating to the handling of antimicrobial waste can also be introduced into rules relating to the handling, use and disposal of wastewater treatment products. Furthermore, wastewater laws often include provisions relating to the siting, construction, operation and decommissioning of wastewater systems (FAO, 2009), to ensure effective functioning of the system. For example, in the Act just mentioned from Mauritius, the design and construction of any wastewater system requires the approval, and in some cases, the supervision, of the competent authority (Section 42).

8.2.10. Preventing and addressing pollution: a focus on waste management

Overview of key regulatory elements on waste management relevant for antimicrobial resistance

- Operators who manage waste professionally (collection, transport, treatment and disposal) should be licensed and subject to prescribed duties of care
- Specific antimicrobial waste collection schemes may be imposed for the return of leftovers, containers, etc to veterinary clinics and pharmacies.
- Legislative mechanisms that incentivise a circular economy or waste prevention and reduction may reduce volumes and toxicity of waste
- Legislative provisions on municipal solid waste landfills management may include mechanisms that prevent AMR-related pollutants from leaching into nearby soils and water bodies.

Rationale

Waste from manufacturing antimicrobials, or use of antimicrobials in agriculture or human waste, is discharged to varying degrees into the environment. Waste should be prevented, and where generated, it should be treated before release into any environmental media. While treatment may be an option, particularly for municipal waste or wastewater, the WHO has cautioned that some biological treatment processes may exacerbate the development of antimicrobial-resistant microorganisms and the acquisition of resistance genes (WHO, 2014). Furthermore, the disposal of unused or expired antimicrobials (as well as their packaging) may result in build-up in the environment. Thus, any legislative provisions that seek to reduce, eliminate and regulate waste, may be used to reduce the environmental dimensions of AMR.

Common features of waste laws

Different types of waste require different methods of disposal. Legal frameworks may establish mechanisms to reduce, eliminate or otherwise regulate different types of waste. Legislative provisions cover treatment, storage, transport, and disposal of waste with a view to preventing harm to humans and the environment. Waste disposal should follow procedures prescribed by the competent authority. These laws already provide, among other aspects, the infrastructure (institutional machinery and inspections systems) to monitor discharges and build-up of contaminants in the environment. The enforcement and monitoring mechanisms, as well as the requirements and standards established in these types of laws can be used to introduce AMR parameters into the framework.

Operators that treat and manage waste

Persons that carry out waste transport, handling and treatment professionally are required to be in possession of a permit authorising such activity. The competent authority should keep a register of all such businesses. Legislation typically sets out detailed criteria for the approval of such permits, including the infrastructure, design and construction requirements, and EIA reports.

Permits may carry conditions. In Section 22 of Saint Lucia's *Waste Management Act (No. 18 of 2004)* conditions include compliance with design and operating standards for the type of waste handled (set out in Schedules to the Act). These Schedules contain further stipulations; for example, in relation to biomedical waste, at a biomedical waste treatment facility may only receive waste from an authorized hauler and where the waste is packaged in accordance with relevant transportation guidelines.

Waste legislation may impose specific duties of care for operators that handle antimicrobials and antimicrobial waste. Waste management operators are often under extensive document and record-keeping obligations. Specific requirements may be added to a (subsidiary) legal framework to include AMR-specific information, such as notifications and reporting, and rules on handling, storage, transport, and disposal.

Take-back schemes

Legislation may target antimicrobial emissions from unused and expired pharmaceuticals through specific waste collection schemes (such as waste medicines collected by veterinary pharmacies and clinics). These activities are typically exempt from permit and registration requirements relating to waste management. As part of the marketing authorization process for a VMP, EU *Regulation 2019/6 on veterinary medicinal products* requires the information on the use of take-back schemes for the disposal of unused VMPs or waste, and where necessary, additional precautions regarding hazardous waste.

Waste prevention and reduction

Recent environmental and waste laws are increasingly adopting mechanisms to encourage a circular economy that requires and incentivizes waste prevention and reduction, including mechanisms for safe collection and disposal/destruction of waste. In some cases, laws may stipulate a time within which waste must be re-used, recycled, treated or disposed. A cradle-to-grave approach for antimicrobials, means that waste prevention and reduction measures are taken into account from the initial design of the product and through the stages of treatment and disposal at its end-of-life. Kenya's *Sustainable Waste Management Act (No. 31 of 2022*), which promotes sustainable waste management and circular economy practices for green growth, establishes the "zero waste principle" which calls for products and processes to be designed and managed to reduce the volume and toxicity of waste and materials, and to conserve and recover all resources to treat waste as a resource (Section 4).

Legislative trends towards holding businesses to account for the impacts and externalities of their supply chains is also on the rise. In addition, largely through voluntary initiatives relating to business sustainability initiatives, pharmaceutical companies have already started to impose restrictions on their suppliers of antibiotics and APIs, with respect to limiting contamination around their manufacturing or processing sites (ReAct, 2019). Obligations may vary under law for manufacturers, importers, distributors or product designers relating to disposal/management of waste from their products. For example, manufacturers of antimicrobials may be required to provide labelling instructions and the means for the safe disposal of antimicrobials and their containers and packaging. Requirements relating to labels during registration processes (see Section 8.1.5 and 8.1.11 of this Study) should include appropriate instructions for safe disposal and destruction.

Pollution from municipal landfills

Legislation governing municipal waste plans may include the imposition of rules relating to waste separation schemes (so that waste streams are sorted at source), and for residual waste to be progressively reduced. Nonetheless, the UNEP has highlighted the role of landfills containing municipal solid waste as a reservoir for the development and transmission of AMR; this is exacerbated in places where there is high population density and poor solid waste management (UNEP, 2022). Furthermore, it was noted that landfill leachate generally contains significant antimicrobial-resistant microorganisms and is also rich in other contaminants that stress microorganisms, thereby potentially contaminating surface and groundwater as well (UNEP, 2022). Accordingly, legislation addressing the management of solid waste landfills may also include appropriate provisions regarding how antimicrobial wastes are disposed. More broadly however, legislation often contains requirements regarding the siting and construction of landfills to minimize leachate and stormwater damage. Saint Lucia's *Waste Management Act (No. 18 of 2004)* calls for landfill designs to ensure that watercourses that cross the site can be diverted, as can any surface water that may enter the landfill.

Legislation may also mandate that municipal management plans address the management, financing and operation of waste treatment and disposal infrastructures at municipal level. Such plans may include the allocation of responsibilities between public and private actors carrying out waste management, as well as any waste disposal awareness campaigns that should be directed at the general public. Section 9 of Kenya's *Sustainable Waste Management Act (No. 31 of 2022*) establishes specific roles and responsibilities for county governments, including: developing county-specific legislation on waste management in conformity with the Act, establishing infrastructure that promotes segregation, maintaining data on waste management activities, managing designated landfills, and entering into inter-county cooperation agreements for waste management. In order to encourage compliance, the Act calls for a partnership programme for continuous eduction targeting waste generating industries and sectors.

9. Minimizing the need for antimicrobials

Maintaining the health of plants, livestock and aquatic animals used for food production, and good management practices which strengthen the health of these agricultural resources, reduces the need for antimicrobials in the first place. The regulatory frameworks for pest and disease prevention, surveillance and control therefore assume particular significance in this regard.

9.1. Animal health, production and welfare: role in antimicrobial resistance

It is estimated that two-thirds of the increase in antimicrobial use in coming years will occur due to animal production (Van Boeckel *et al*., 2015). In this context, the diversity in existing production systems and animal species vis-à-vis their eco-geographical location are relevant: there is data to suggest that extensive and smallholder livestock production systems appear to use relatively small amounts of antimicrobials, mostly for therapeutic use and not for prevention or growth promotion (FAO, 2016). Intensive swine and cattle production are the most significant users of antimicrobials (Grace, 2015), along with intensive poultry and aquaculture production. As demand for foods of animal origin is projected to increase in the coming years, this could result in a correlated rise in the use of antimicrobials.

In combination with good animal production practices, a robust animal health system is designed to optimize physical and behavioural health and welfare of animals, and includes the prevention, treatment and control of diseases (Glossary, TAHC). Animal health and animal production are strongly interlinked and the quality of animal production practices impact on animal health. Accordingly, risk-based animal health measures should be implemented alongside good animal husbandry practices. Animal health legislation is designed to prevent the introduction and spread of diseases and equip the jurisdiction with mechanisms for control and eradication. This system is supported by surveillance infrastructure, systems for traceability of animals, animal welfare requirements, and appropriate monitoring and control of animal slaughter and animal production premises.

9.1.1. Animal health

Overview of key regulatory elements on waste management relevant for antimicrobial resistance

- Legislation should define key terms used in the law in accordance with the *Terrestrial Animal Health Code* and the *Aquatic Animal Health Code* produced by the World Organisation for Animal Health. Using these instruments as a guide ensures that measures are taken on appropriate commodities. Some countries may include antimicrobial-resistant microorganisms in certain definitions to enable actions by authorities.
- The law should identify a competent authority responsible for animal health matters, as follows:
  - with a chain of command that lists responsibilities and appropriate coordination mechanisms of all authorities (including at decentralized levels) that are involved in animal health and welfare matters;
  - clear provisions for coordination and information exchange, particularly on matters relating to veterinary public health, including food safety, zoonoses and antimicrobial resistance (AMR).

Overview of key regulatory elements on waste management relevant for antimicrobial resistance (cont.)

- The law should designate reference, official and authorized laboratories for animal health (which can also be used for AMR surveillance).
- Legislation should require the development of a list of notifiable or listed diseases by the competent authority.
- Legal provisions for surveillance for animal diseases should include an early detection system (such mechanisms may be used for AMR-related surveillance).
- Legislation may impose a duty to report a notifiable or listed disease by veterinarians and veterinary paraprofessionals, farmers, researchers or other stakeholders.
- Legislation should empower the competent authority to respond, in proportion to the risk, of an animal disease outbreak or emergency, with correlated powers (e.g. movement restrictions, compulsory treatments, preventive culling).
- Legislation may set up a system for animal identification and traceability; such a system may be linked with that used for food safety.

Scope and definitions

The manner in which key terms are defined in the legislation affects the scope of coverage, the actions that may be taken, who can take the action, and the commodities covered. Thus, definitions of animals, animal products, vectors and fomites (i.e. items capable of harbouring a disease or infectious organism such as equipment, straw bedding, etc.) should be defined to fall within the scope of the law. The Glossaries accompanying the TAHC and the AAHC may be used to guide national laws and enable harmonization with international standards. Notably, *Regulation (EU) 2016/429,* which creates a legal framework for animal disease prevention in the European Union explicitly considers microorganisms that have developed resistance to antimicrobials to be treated as if they were transmissible diseases, and as such are covered in the scope of the Regulation.

Functions of the competent authority on animal health and veterinary public health

Chapter 3.4 of the TAHC calls for legislation to identify the competent authority responsible for animal health and welfare, and to enumerate its powers and functions. Guyana's *Animal Health Act (No. 7 of 2011)* establishes the Guyana Livestock Development Authority (Section 3) and tasks it with functions such as preventing and controlling the introduction, establishment or spread of prescribed diseases and national pathogens, and for that purpose carry out surveillance, monitoring, official control and stamping-out programmes (Section 4).

Legislation should designate a body of veterinary inspectors to support the enforcement and implementation of animal health requirements and grant such inspectors the necessary powers to carry out their duties, as prescribed in Article 3.4.5 of the TAHC. From an AMR perspective, the requirement of a chain of command in the institutional structure as prescribed in Article 3.4.2 of the TAHC, allows for the coverage of AMR dimensions at all these levels. To this end, the Article includes a clear delineation of the responsibilities of various authorities involved in disease control and trade from the central level to field level. Coordination and cooperation frameworks should be in place where multiple competent authorities are involved, for example in relation to environmental, food safety or other public health matters (Article 3.4.5 of the TAHC). Under the *Animal Health Act (No. 12 of 2017)* of Antigua and Barbuda, the animal health authority is tasked with coordinating the inspections of slaughterhouses together with food safety authorities, and also with monitoring the distribution of VMPs in coordination with the ministry responsible for health (Article 5).

Coordination frameworks for the purposes of information exchange and dissemination, consultation and policy development may include *inter alia*: (i) advisory bodies (with public and private stakeholders); or (ii) executive bodies (comprising public officials only). In the Bahamas, the *Animal Health and Production Act (No. 7 of 2016)* establishes an Animal Health Advisory Committee, which includes representatives from the ministries responsible for health and the environment, as well as representatives from the veterinary association and animal producers (Section 8). In addition, MoUs, service level agreements, or other similar arrangements may be used to cement cooperation and information exchange responsibilities among competent authorities. Cooperation can also take place in the form of joint inspections and delegated functions. Whatever the cooperation mechanism, it is important to ensure that the responsibilities and duties for the exchange of specific information are clearly delineated.

An example of such cooperation takes place within the realm of veterinary public health on matters of food safety, zoonoses and other aspects at the intersection of human health and animal health. The authority responsible for veterinary matters should collaborate with the food safety authority on matters relating to the safety of foods of animal origin, including: most specifically on the identification of animals and traceability of animal products for human consumption; safety of feed; ante-mortem and post-mortem inspections of food-producing animals; and the setting and enforcing of MRLs for antimicrobial residues, among other contaminants. In the Bahamas, the *Animal Health and Production Act (No. 7 of 2016)* contains express provision for the collaboration between veterinary and health authorities on zoonoses, and veterinary and food safety authorities on foods of animal origin (Section 4). In Sweden, under the *Regulation on the monitoring of zoonoses and zoonotic agents in animals and in food (2005: 422)*, cooperation among the authorities responsible for food safety and veterinary matters is extended to data collection over AMR. Section 7 of the Regulation holds the Swedish National Board of Agriculture, the Swedish National Food Administration and the National Veterinary Institute responsible for collecting comparable data on the occurrence of AMR in zoonotic infectious agents.

Legislative frameworks for laboratories are also critical for AMR surveillance. An existing laboratory infrastructure for animal health may be used in support of AMR surveillance in the animal health sector, which in turn feeds into the national level AMR surveillance structure. According to Article 3.4.7 of the TAHC, legislation should make provision for the roles, responsibilities, obligations and quality requirements of: (i) reference laboratories; (ii) laboratories for the analysis of official samples; and (iii) laboratories that conduct safety and quality control testing. The law should officially recognize laboratories that carry out analyses of official samples, and those that validate results or carry out quality control. Laboratories can be public or private, or even be located outside the country, provided in all cases that there is recognition and designation as an official laboratory by the competent authority in accordance with the law.

The competent authority is also responsible for establishing animal health measures. In the Lao People's Democratic Republic, the *Decree on the Prevention and Control of Animal Diseases (No. 228 of 2012)* stipulates that disease prevention and control measures shall: "(a) be applied to the extent necessary to protect animal health, (b) be based on risk assessment and be proportional to such risk; and (c) be not more stringent than necessary to meet the objectives of this Decree and shall not create unnecessary barriers to trade;…". The WTO's *Agreement for the Application of Sanitary and Phytosanitary Measures (SPS Agreement)* calls for all measures to be scientifically justified, based on risk analysis, and the least restrictive means of achieving the country's appropriate level of protection. The SPS Agreement also espouses the application of the principles of necessity and proportionality for the setting of animal health measures. This means that disease risks, as well as treatment with antimicrobials versus alternatives, would be subject to an assessment prior to the adoption of response measures (see Chapter 6.11 of the TAHC).

Listed diseases and correlated powers

Article 3.4.9 of the TAHC calls for veterinary legislation to empower the competent authority to manage diseases of importance to the country, and specifically to develop a list of those diseases, guided by the recommendations in Chapters 1.1 and 1.2 of the TAHC. Likewise, Article 1.2.2 of the AAHC establishes the criteria for listing diseases in aquatic animals. The WOAH Members are required to report certain diseases. The veterinary authority should be legally empowered to act where a notifiable disease is suspected or confirmed, so as to contain the spread of disease through immediate action in relation to an animal or premises. The authority must be endowed with significant powers to stop and control movements of animals, animal products, etc., during an animal disease emergency. Laws must contain clear procedural safeguards by setting out the procedures to be followed and who is responsible for taking action. Kenya's *Animal Diseases Act (as amended in 2012)* grants the competent authority the power to declare an infected area (and set its geographical limits), as well as set out the measures and restrictions applicable within such area, such as movement prohibitions without authorization and the destruction of carcasses of diseased animals in a specified manner.

Surveillance and early warning systems

Surveillance of AMR is a key pillar of the Global Action Plan. Surveillance under animal health systems provide the competent authority with a technical basis for the development and implementation of animal disease control. Article 1.4.1 of the TAHC recognises *animal disease* surveillance as a tool to monitor disease trends, to facilitate the control of disease or infection, to provide data for use in risk analysis (for animal or public health purposes), and to substantiate the rationale for animal health measures. The Seychelles' *Animal and Plant Biosecurity Act 2014,* tasks the competent authority with carrying out surveillance of pests and diseases, as well as to assessing the status of regulated pests and diseases in the country (Section 5).

The European Medicines Agency works closely with the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC) to analyse the potential relationship between the consumption of antimicrobials by humans and animals and the occurrence of antimicrobial resistance. The European Union agencies deliver their findings in joint inter-agency antimicrobial consumption and resistance analysis (JIACRA) reports.

Legislative provisions that enable the collection, transmission, dissemination and utilization of epidemiological data (Article 3.4.9 of the TAHC) can later be used for AMR surveillance purposes. Legislation should set up a framework for an early detection system to detect animal diseases that is aligned with the WOAH standards on disease surveillance systems (see Article 1.4.5 and Article 1.4.6 of the TAHC; Article 1.4.5 of the AAHC). Zambia's *Animal Health Act (No. 27 of 2010)* requires the establishment of an early warning system for the purposes of early detection of diseases (Section 53).

While the TAHC and the AAHC set out general standards on disease surveillance systems, Chapter 6.8 of the TAHC establishes standards for surveillance and monitoring specific to AMR. Both the TAHC and the AAHC indicate that some surveillance systems are primarily established as early detection systems but may also provide valuable information to demonstrate freedom from infection. Early detection of animal diseases also facilitates rapid responses, as well as a basic level of good health that mitigates the need for VMPs. As early detection of diseases is a key element of surveillance, legislation should include a general duty on the public and veterinarians to report notifiable diseases. Ethiopia's *Proclamation on Animal Health and Welfare (2012)* contains a number of general provisions regarding surveillance for animal diseases under which AMR parameters may also be covered. It is sufficient to create provisions such as those found in this Act, for example: the competent authority is empowered to establish an animal disease surveillance system and creates a network of public and private veterinary professionals, animal owners and other persons

and institutions to support the system (Section 13). This system includes prescribed roles at various tiers of government, including regional veterinary authorities (Section 6). While this system is specific to notifiable and emerging animal diseases, the disease surveillance infrastructure may be modified and expanded to encompass greater AMR elements.

National programmes to monitor AMR in agriculture provide critical data to understand and inform the design of measures that the specific context requires to reduce antimicrobial use. The competent authority should have the power to gather relevant data as well as the financial, technical and equipment resources to manage and analyse the data. Monitoring programmes should also gauge the use and circulation of antimicrobials in the country, identifying AMR prevalence and patterns, and supporting determinations on effectiveness and geographical spread of antimicrobial use.

Disease response measures

Legislation should allow for measures to be taken to address all identified risks to human or animal health (Article 3.4.9 of the TAHC). To ensure a One Health approach in preventing and controlling animal diseases which are transmissible to animals or to humans, *Regulation (EU) 2016/429* requires that its rules are to be interpreted by taking into account the relationship between animal health and: public health; the environment; food and feed safety; animal welfare; AMR; and food security (Article 1(2)). Where a veterinary inspector detects or suspects a notifiable disease, he or she should be empowered by law to take measures to contain and eradicate the disease.

Legislation may outline the following disease control measures:

- Prohibiting or controlling of animals, animal products and potentially disease-carrying items (animal-related items), as well as persons and vehicles into or out of established geographic perimeters or zones set up by the authority.
- Treating or seizing, killing and disposing of animals, animal products and animal-related items where required.
- Compensation to animal owners where feasible based on pre-established parameters.
- Vaccination programmes, which can be entirely publicly financed, privately funded or mixed, and can be species-specific, area- zone- or compartment-specific, and progressively implemented according to resources.

Possible response measures also include the sanitation and disinfection of premises, including equipment, vehicles and other objects (the veterinary authority may stipulate the procedures for disinfection, the types of disinfectants, etc). The types of disinfectants which can be used for disease control may impact AMR and thus should be authorized by the competent authority. The United Kingdom's *Diseases of Animals Approval of Disinfectants Order (Northern Ireland) Order SR 272 of 2008* stipulates that only approved disinfectants must be used. This Order also sets out rules relative to the use of such disinfectants and identifies the authority that may approve a disinfectant in accordance with this Order. The Order also prohibits the placing of any disinfectant on the market that is labelled or otherwise represented as an approved disinfectant, if it is not approved under this Order or if the formula for it has changed since approval was granted.

Where the disease situation has been elevated to a disease outbreak or animal health emergency by the competent authority, the latter or the responsible minister may declare an emergency. Legislation should require the establishment of an emergency response plan. During emergencies, the measures imposed may be stronger and more restrictive, but should be proportionate, technically justified and time bound.

Identification and traceability systems

Identification and traceability systems for animal health purposes can contribute to AMR surveillance as these systems facilitate the traceability and control of animal movements and require record-keeping by the animal owner. For aquatic animal products, a simple provision requiring traceability may be included in legislation, and often traceability is managed at farm-level by the aquaculture producer. Nonetheless, legislative provisions for identification and traceability usually govern terrestrial animals, and limited resources may mean the system applies only to certain species or perhaps a progressive implementation approach is used as more resources become available. Namibia's approach under its *Animal Health Act (No. 1 of 2011)* is to restrict application of the law to prescribed animals, as decided by the minister responsible for animal health on the recommendation of the Chief Veterinary Officer (Article 23).

Identification and traceability systems may vary in scope and function (animal health, food safety, etc.) and relevant guidance is set out in Article 4.3.3 of the TAHC. Identification and traceability mechanisms often entail cooperation between animal health and public health/food safety authorities for foods of animal origin. This is the case in Antigua and Barbuda, where the *Animal Health Act No. 12 of 2017* requires the competent authority for animal health to set up a system for the identification and traceability of animals and to collaborate with the authority responsible for food safety regarding the traceability of animals and animal products to be used as food for human consumption (Section 24).

Legislation often allows for the exchange of information between these bodies, ensuring there is provision made for confidentiality of information collected and a limitation on the use that can be made of the information gathered.

Imports and exports

Preventing the introduction of diseases into the country will help reduce or remove the need to apply antimicrobials and other treatment for the (imported) disease. Import controls should also be aligned with the SPS Agreement and reflect its provisions (i.e. primarily that import measures are based on international standards or risk assessments). Legislative provisions for imports typically prohibit imports of aquatic or terrestrial animals, as well as their products and other items, that harbour notifiable diseases. All animals and some animal products require veterinary certificates to be imported. These documentary requirements are supported by risk-based inspection systems. The law may set out actions to be taken when an imported shipment does not comply with requirements. Chapter 5 of both the TAHC and the AAHC set out specifics on animal health measures applicable to pre-shipment and at the border. The AAHC in Chapter 5.5 includes some specifics pertinent to aquatic species such as the control of risks associated with the transport of aquatic animals.

Export controls are designed to meet the requirements of the importing country. Following inspections, export of animals (international veterinary) may be issued according to the requirements of the importing country. Under EU *Regulation 2019/6*, rules relating to the production methods used for animals or products of animal origin to be imported into the European Union shall apply, mutatis mutandis, to operators in third countries and those operators shall not use the antimicrobials prescribed under Article 37(5).

Export procedures should be aligned with Chapter 5.2 of both the TAHC and the AAHC. Importing countries may require that certain treatment protocols are to be followed, including the use or not of certain antimicrobials, as well as any withdrawal periods, or other management practices that may be relevant for antimicrobial use. The establishment of compartments and free zones by the competent authority are designed to eradicate certain types of disease and thus favour the export process. Legislation may set out the principles and mechanisms to establish and operationalize zones and compartments using the elements outlined in Chapter 4.3 and 4.4 of the TAHC for terrestrial animals and in Chapter 4.1 of the AAHC for aquatic animals.

9.1.2. Animal production

Overview of key regulatory elements for animal production relevant for antimicrobial resistance

- Some jurisdictions require all farms to be registered while many jurisdictions make this requirement only of large-scale (commercial) farms.
- Legislation may impose inspections to enable oversight of activities on farms.
- Legislation may establish biosecurity-related requirements relating to:
  - design, construction and siting;
  - production and hygiene practices, including prudent use of antimicrobials.
- Legislation may impose record-keeping and reporting obligations on farmers which may offer a legislative hook to include reporting on antimicrobial use.
- Legislation may establish specific roles for extension services or local animal health workers to disseminate good practices in relation to biosecurity practices (and therefore prudent antimicrobial use) and good animal husbandry.
- Legislation may establish a legal foundation for the adoption of good agricultural practices, good husbandry practices, good production practices, and related good farming practices.

Farm registration

Registration of farms by the competent authority allows control over the activities that take place in those establishments. Furthermore, requirements associated with registration may enable greater control over the antimicrobial use that takes place on terrestrial and aquatic farms. It is noted however, that animal production activities or establishments are not subject to formal registration requirements in many jurisdictions. In these countries, inspections and extension services may serve to assist in aligning the practices at these establishments with established good practices. Viet Nam's *Decision 46/2005/QD-BNN* establishes the subjects of veterinary hygiene inspection which targets various kinds of bacteria, hormones, toxic gases, radioactive substances, antibiotics, and other substances (Section 1). Within the Decision's scope are animals, animal products, and animal feeds, among other items (Section 2). Section 3 provides a list of subjects liable to veterinary hygiene inspection and to compulsory application of veterinary hygiene standards that include animals for slaughter, food, establishments which process and preserve animal products, means of transport for animal products, etc.

Pertinent rules in legislation that can be used to link registration to AMR control can come in the form of stipulations on the siting, construction, design and layout of terrestrial or aquatic farms. These rules reduce overcrowding and prevent animal diseases, which in turn reduce the need for antimicrobials. Design stipulations also take into account the best ways to manage disposal of waste as well as good biosecurity practices during operations. In addition, requiring specific water facilities and water use processes can positively affect management of the farm or aquaculture facility. Farm registration conditions can be used as a legal basis on which to add duties relating to: (i) the application of specific production practices to reduce the need for antimicrobials; (ii) reporting quantities of antimicrobial use and incidences of adverse effects; and (iii) compliance with inspections to enable oversight of good practices.

Biosecurity measures, good hygiene and good husbandry practices

Meaningful reduction in antimicrobial use will only be achieved in a context where farmers improve production practices to promote health, hygiene and animal welfare. Thus, animal health or animal production legislation should contain clear responsibilities for animal owners to implement good husbandry and production practices, and to implement hygiene and animal welfare requirements. The *Guide to*

Good Farming Practices for Animal Production Food Safety (FAO and OIE, 2010) and Article 3.4.8 of the TAHC provide guidance on good on-farm practices. In this Study, Box 9 sets out the Codex CXC 61-2005 listing of the responsibilities ascribed to owners of food-producing animals. Biosecurity measures include features such as: prescribed construction and design (e.g. spaces to separate sick and healthy animals, separate birthing areas and adequate ventilation in closed spaces); limiting the access of people and wildlife to facilities; using VMPs as prescribed; and establishing good waste management practices. Good agricultural practices (GAP), good husbandry practices (GHP), and good production practices (GPP) often feature similar elements. Some specific provisions of these practices may work towards minimizing the transmission of microbes or contamination with antimicrobials, such as the handling of manure and other items containing antimicrobials, and correct disposal practices. While the specific technical recommendations of these guidelines would not frequently feature in legislation, the latter may indicate in general terms that these production practices should be applied. In such cases, often simple legislative clauses stating that the competent authority will elaborate appropriate guidelines will suffice. As a final note, some types of production practices or schemes that result in particular certifications relating to production processes (i.e. organic or agroecological certifications) may prohibit or restrict the use of VMPs (as well as pesticides, feed additives and other prescribed agricultural inputs) as a condition of certification. These are often general stipulations on practices relating to VMPs, such as prohibiting VMPs in the case of organic farming or minimizing use in the case of agroecology systems.

In addition, legislative provisions that set out the role of veterinary extension services (in veterinary legislation or general agricultural laws), or the role of local animal health workers, contributes to securing compliance with good practices and prudent use of antimicrobials. Similar legislative provisions involve empowering the competent authority to raise awareness and initiate information dissemination campaigns that can also focus on antimicrobial and VMP use. Such provisions would target veterinarians, local animal health workers and farmers (particularly poultry farmers and aquaculture producers).

As some practices may require structural changes on farms that may be costly to implement, legislation may offer financial support (including tax subsidies) and technical advice for qualifying farmers to make these biosecurity-related changes on their premises.

Finally, animal health and disease control legislation typically identify core responsibilities for owners of animals under their care, as well as the functions of the competent authority for veterinary matters relating to the animal health status of the country as a whole. Legislative requirements on animal owners include the duty to report animals infected with a notifiable disease and to segregate sick animals from healthy ones. Kenya's *Animal Diseases Act (as amended in 2012)* places responsibility on owners of animals infected with a notifiable disease to separate sick and healthy animals and to notify the nearest authority.

Box 9. Code of Practice to Minimize and Contain Foodborne Antimicrobial Resistance (CXC 61-2005)

Producers of food-producing animals have the following responsibilities:

- To use antimicrobial agents only when necessary, under the supervision of a veterinarian or plant/crop health professional when required, and not as a replacement for good management and farm hygiene, or other disease prevention methods;
- To implement a health plan in cooperation with the veterinarian, plant/crop health professional, or other suitable trained person authorized in accordance with national legislation that outlines preventative measures;
- To use antimicrobial agents in the species, for the uses and at the doses on the approved labels and in accordance with the prescription, product label instructions or the advice of a veterinarian, plant/crop health professional or other suitable trained person authorized in accordance with national legislation familiar with the food-producing animals or the plant/crop production site;
- To isolate sick and dying animals, dispose of dead animals, diseased plants/crops promptly under approved condition by competent authorities;
- To comply with the storage conditions of antimicrobial agents according to the approved product labelling;
- To comply with the recommended withdrawal periods or pre-harvest intervals;
- To not use out-of-date antimicrobial agents and to dispose of all unused or out-of-date antimicrobial agents in accordance with the provisions on the product labels and national legislation;
- To inform the veterinarian, plant/crop health professional, or other suitably trained person authorized in accordance with national legislation in charge of the production unit of recurrent disease problems or suspected lack of efficacy of antimicrobial applications;
- To maintain or have their veterinwarian, plant/crop health professional, or other suitable trained individual maintain all clinical and laboratory records of microbiological diagnosis and susceptibility testing. These data should be made available to the professional in charge of the administration in order to optimize the use of antimicrobial agents.
- To keep adequate records of all antimicrobial agents used, including, for example, the following:
  - copy of the prescription, order for application or other documentation, when available;
  - name of the antimicrobial agent/active substance and batch number;
  - name of supplier;
  - date of administration; species and number of animals or plants/crops;
  - identification of the production unit to which the antimicrobial agent was administered;
  - disease treated, prevented, or controlled;
  - relevant information on animals or plants/crops treated (number, age, weight);
  - quantity/dose and duration of the antimicrobial agent administered;
  - withdrawal periods or pre-harvest intervals;
  - result of treatment, in consultation with the veterinarian or plant/crop health professional; and
  - name of the prescribing veterinarian, plant/crop health professional or other suitably trained person authorized in accordance with national legislation.
- To ensure sound management of wastes and other materials to minimize dissemination of excreted antimicrobial agents, resistant microorganisms and resistance determinants into the environment;
- To address on-farm biosecurity measures and take infection prevention and control measures as appropriate and as provided in the WOAH *Terrestrial Animal Health Code* and the *Aquatic Animal Health Code*;
- To participate in training on issues related to antimicrobial resistance and the responsible use of antimicrobial agents;
- To assist the relevant authorities in surveillance programmes related to antimicrobial use and antimicrobial resistance, as appropriate.

Source: Adapted from *CXC 61-2005, Codex Alimentarius, 2005 (as amended in 2021).*

While the previously mentioned instruments set out the basic framework provisions that should find a legal basis in primary legislation, more technical details may be more appropriately relegated to manuals, codes of practice or other lower-level instruments. The latter may be more readily updated in line with evolving best practices and advances in technology and science. Regional-level instruments such as the ASEAN *Good Animal Husbandry Practices for Layers and Broilers: Food Safety Module* focuses on minimizing food safety incidents, but also covers elements of biosecurity, workers' health and safety, animal welfare, and measures to reduce environmental impact. These guidelines set out a range of practices and measures to prevent disease and for effective herd management, including: (i) regularly checking animals for signs of disease, reducing contact between healthy animals and potentially infected animals; (ii) maintaining an appropriate population density for the species and age group in question, either by following locally enforceable measures or by obtaining appropriate advice from recognized experts; (iii) maintaining the hygiene and safety of all facilities and establishing hygienic working procedures in order to minimize the risk of introduction of pathogens and contaminants; (iv) taking all appropriate measures to prevent contamination by vehicles; (v) giving personnel appropriate hygiene equipment and disease prevention treatment; and (vi) ensuring overall health of livestock through good nutrition and reducing stress. Design and construction elements are also important, as follows: (i) ensuring that where animals are confined, the housing or pens are constructed such that the basic needs of animals are fulfilled, especially with regard to ventilation, drainage, and manure removal; (ii) ensuring that walking surfaces are level, non-slip, and all surfaces should ideally be washable; and (iii) locating farms in areas free from industrial and other pollution, and sources of contamination and infection.

Specific considerations for the management of manure

Animal manure is often used as fertilizer for crop fields. However, manure from animals that have been recently treated with antimicrobials should not be used as organic fertilizer, as the amount absorbed by an individual animal ranges widely and can be as low as 10 percent of the administered dose, with the remainder excreted as active compounds (FAO and WHO, 2019). Manure may remedy nutrient poor soils but may also result in soil and surface and groundwater contamination if not treated and managed appropriately.

A greater understanding of the persistence dynamics of antimicrobial-resistant bacteria, antimicrobial residues, ARGs and the potential for exchange of ARGs in human and animal wastes and wastewater, and how these factors vary with treatment, will allow for the more precise assessment of risks associated with environmental sources of food contamination (FAO and WHO, 2018).

Legislation may establish the appropriate treatment methods and the observation of specific holding times (both before such waste (manure) is applied and also before animals are allowed onto treated pastures). Legislation should also prohibit the use of animal and human waste on plants intended for direct human consumption unless the waste has been appropriately treated first. Suggested holding times are directly related to climatic conditions in a particular region (pathogen die-off is faster at higher temperatures). Wastewater should also not be used on plants intended for direct human consumption unless the wastewater has been appropriately treated. In the United Kingdom, the *Sludge (Use in Agriculture) Regulations (1989)* places a waiting period for certain activities after the application of sludge on agricultural land. For agricultural land used for grazing animals or harvesting forage crops, the Regulations require a period of three weeks commencing on the date of the use. For harvesting fruit and vegetable crops that are grown in direct contact with the soil and are normally eaten raw, the waiting period should be ten months commencing on the date of the use (Regulation 4).

9.1.3. Animal welfare

Overview of key regulatory elements for animal production relevant for antimicrobial resistance

- Legislation should establish cruelty as an offence and offer a legal definition of the term "animal cruelty".
- Legislation on animal welfare may include requirements relating to housing, transportation, slaughter and killing, draught animals, etc., with special clauses that target certain species or production systems.
- While not detailing specifics, legislation may contain principles relating to: suitable shelter, including construction and materials used; feed and water; environmental and space/density conditions; and principles for handling, controlling and caring for animals throughout their lives.

Rationale

Neglect of animal needs for appropriate feed, water, shelter and other aspects leads to increased risk of disease, infections and injury, and results in poor quality or contaminated foods of animal origin. More specifically, high density of animals in pens or stables contributes to high infection pressure. Thus, ensuring animal welfare is a means to reduce the use of antimicrobials that are required to remedy disease and poor production practices.

Requirements

Legislation can set out basics relating to prohibitions against cruelty and the framework for welfare, including specific rules for animal housing, husbandry, transportation or slaughter, among others. Article 3.4.10 of the TAHC declares that welfare laws should provide a basis for actions to address the animal welfare-related requirements set out in Section 7 of the TAHC and of the AAHC. These provisions establish basic principles relating to farm animal production, including housing, transport, slaughter, handling, feed, and water. These standards incorporate elements of the globally recognized "Five Freedoms" animal welfare principles, which include: (i) freedom from hunger and thirst; (ii) freedom from discomfort; (iii) freedom from pain, injury or disease; (iv) freedom to express normal behaviour; and (v) freedom from fear and distress (Farm Animal Welfare Council, 2009). The *Codex Alimentarius* also recognizes that good animal feeding contributes to animal health and welfare. The Codex has issued a number of texts relating to animal feed for the production of safe and quality products of animal origin, among these the *Code of Practice on Good Animal Feeding (CXC 54-2004)*.

Any person who owns, cares for, handles, uses, transports, or sells any animal should be responsible for ensuring that its welfare needs are met. In Malaysia, under the *Animal Welfare Act 2015 (Act 772)*, certain activities as specified in the Act require a licence (Section 15). Holders of such licences are charged with the duty of taking reasonable steps to ensure that the needs of their animal are fulfilled. These needs are further listed in the Act as: (i) a suitable environment; (ii) a suitable diet; (iii) the ability to exhibit its normal behavioural patterns; (iv) housing apart from other animals; and (v) the need to protect from pain, suffering, injury and illness (Section 24). In the Australian state of New South Wales, the *Prevention of Cruelty to Animals Act 1979 (last amended in 2020)* requires that all animals be provided with food, drink and shelter (Section 8) as well as opportunities for adequate exercise (Section 9). Similarly, in New Zealand, the *Animal Welfare Act (1999)* places on owners the responsibility of ensuring the physical, health and behavioural needs of an animal, as well as the obligation to protect the animal from disease and to ensure rapid diagnosis of disease (Section 10 and 11).

Given that high density of animals in stables and pens contributes to the rapid spread of disease among the population, the TAHC provisions on housing warrant closer attention. A number of different requirements may apply depending upon whether animals are kept outdoors or indoors. Regulations or manuals should address the type and condition of the accommodations in which animals are kept. In practice, this will vary considerably depending upon the species. However, a number of basic principles apply to all animals. The key issues are: (i) suitable shelter from the weather; (ii) feed; (iii) water; (iii) environmental conditions (temperature, light, humidity, ventilation); (iv) construction and materials used where indoors; (v) basic principles for handling, controlling and caring for animals throughout their lives; and (vi) space/density. The TAHC also sets out specific animal welfare standards for beef cattle production systems (Chapter 7.9); broiler chicken production systems (Chapter 7.10); and dairy cattle production systems (Chapter 7.11).

9.2. Regulation of the veterinary profession

Rationale

One of the key mechanisms by which prudent and responsible use of antimicrobials can be assured is by establishing requirements relating to the issuance of prescriptions, record-keeping and other rules. Such conduct of veterinary professionals may be found in legislation that governs this profession and through the provision of veterinary services. Ensuring the quality and competence of veterinary professionals may also play a role in reducing AMR. Some countries establish a veterinary statutory body (VSB) for this purpose, which the WOAH defines in the TAHC Glossary as an "autonomous regulatory body for veterinarians and veterinary paraprofessionals" (p. ix). Categories of veterinary professionals are also defined in the TAHC. Other countries may regulate the profession via a government body and include relevant rules in legislation governing veterinary services or in an animal health law. In some jurisdictions, the conduct of professionals is regulated via Codes of Conduct.

Requirements

As mentioned, a VSB (autonomous self-regulating body) may oversee the practice of the veterinary profession. For example, in South Africa, the *Veterinary and Para-Veterinary Professions Act (as amended in 2012)* establishes the South African Veterinary Council for oversight of veterinarians and para-veterinary professions, including establishing norms and standards for their training and professional conduct. According to Article 3.2.12 of the TAHC, a VSB must be free of political or commercial interests, accountable and transparent.

Important features of legislation governing the veterinary profession are: (i) a definition of the professional categories, i.e. the educational, registration and other requirements for belonging to a certain category of veterinary professional; and (ii) their respective competencies, functions, ethical and professional conduct, and other obligations. According to Article 3.4.6 of the TAHC, legislation should establish the minimum education and training requirements for the veterinary professional categories, and the conditions of recognition of their qualifications. Legislation should typically require the establishment of a register or licensing of these veterinary professionals. The South Africa *Veterinary and Para-Veterinary Professions Regulations (as amended in 2018)* set out the qualifications required to qualify for registration as a veterinarian, as a veterinary specialist, as a para-veterinary professional, as an animal health technician, or as a veterinary technologist. Such persons are required to register with the South African Veterinary Council. In Alberta, Canada, the VSB is regulated under the *Veterinary Profession Act (2000)*. This Act prohibits any person except a registered veterinarian or a permit holder to engage in the practice of veterinary medicine (Section 2) and requires all registered veterinarians and every technologist to be a member of the Association established under the Act (Section 5(1)). Part 5 of the Act contains the main requirements for professional conduct for a veterinarian or technologist.

Provisions relating to which category may issue prescriptions varies from jurisdiction to jurisdiction, based on a range of factors. In countries where the number of qualified veterinarians is too small to service the entire country or animal population of a territory, even where the general rule is that antimicrobial prescriptions are to be issued exclusively by veterinarians, the legislation may set out exceptions and appropriate conditions. For example, legislation may permit trained veterinary paraprofessionals or animal health workers to issue certain classes of antimicrobial prescriptions.

Provisions relating to educational requirements (including continuing professional education), often set out in implementing regulations, may include training relating to the various categories of VMPs, their appropriate use, and the special risks associated with antimicrobials, notably AMR. South Africa's *Veterinary and Para-Veterinary Professions Regulations (as amended in 2018),* relating to the continued professional development of veterinary professions (Act of 2012), requires all registered veterinary professionals who practice or provide professional veterinary services to undertake continued professional development (defined in the Regulations) as a prerequisite for retaining registration under the terms of the Act. The Regulations also govern accreditation and monitoring of continued professional development activities by the South African Veterinary Council.

One of the means for oversight of veterinary professionals is through disciplinary measures, such as investigations and hearings. Laws should set out clear procedures and penalties (such as removing veterinary professionals from the register for misconduct), which enable the VSB to take action for breach of rules of conduct.

A Code of Conduct or Code of Ethics may be used to itemize duties in regard to the issuance of VMPs, curricula requirements relating to VMPs, and any obligations such as relating to specific training or continuous education relating to AMR. For example, the Federation of Veterinarians of Europe (FVE) has adopted a *European Veterinary Code of Conduct (2019)*, which holds as one of its core values that "especially in respect of antimicrobial resistance, veterinarians shall be mindful of the impact the use of veterinary medicinal products may have" (FVE, 2019, p. 14).

9.3. Plant health

Overview of key regulatory elements for plant health

- Plant health laws should contain definitions of key terms that are aligned with the *International Standards for Phytosanitary Measures (ISPMs)* no. 5 and that determine the scope of regulation.
- Legislation should establish a National Plant Protection Organization (NPPO), with its composite units defined, and with responsibilities allocated that mirror the functions outlined in Article IV of the International Plant Protection Convention (IPPC).

Rationale

Plant health refers to "the discipline that utilizes official or legislative approaches to prevent pests and disease-causing organisms to spread into endangered areas, especially through human interaction such as international trade" (CPM, 2016, p. 2). Different jurisdictions use the term plant health interchangeably with phytosanitary matters or plant protection. Plant health laws seek to prevent the introduction and spread of pests and to protect plant resources (including cultivated, wild and aquatic plants) through the implementation of phytosanitary measures. While it is recognized that antimicrobials are applied to crops

in the fight against pests and disease-causing organisms, it is also notable that there is no significant body of information as yet that indicates that plant production systems pose a major risk in the development of AMR (CPM, 2019). However, research is still ongoing as to the specific impacts of antimicrobials used in plant production systems and their role in the development and spread of AMR. Notwithstanding, sound plant health legislation can help countries strengthen their phytosanitary status, prevent the introduction and spread of pests and thereby reduce the need for antimicrobial pesticides and pesticides with antimicrobial effects. Official control measures (phytosanitary measures) are applied to regulated pests to improve the overall plant health status in a country, to contain the occurrence and spread of regulated plant pests, and to reduce the severity of plant pests and disease outbreaks.

Plant health laws also seek to facilitate trade in plants and plant products. Plant health legislation may be used as a means to harmonize a country's phytosanitary measures with international standards and to enable a country to meet its obligations under international agreements, specifically the International Plant Protection Convention (IPPC) and the World Trade Organization's SPS Agreement (see Chapter 3 of this Study). Countries that are not signatory members to the IPPC may nonetheless use the IPPC and its implementing standards as a benchmark to set up their national legislation on plant health.

9.3.1. Where is plant health regulated?

Most countries have specific stand-alone legislation on plant health, or laws on plant protection or phytosanitary matters. However, some countries regulate plant health together with animal health under biosecurity laws, or in addition with food safety matters under SPS laws. Plant protection provisions may also be found in agriculture legislation. Some countries may regulate plant health together with pesticides used for agriculture purposes under plant protection legislation, but this often causes confusion because plant protection legislation normally covers pesticide regulation, which has a separate international standards regime (see Section 7.3 of this Study) and is beyond the mandate of the IPPC. Some of the plant health related issues might be also covered under the environmental and customs legislation.

9.3.2. Key features of plant health legislation

Scope of legislation

Plant health laws should regulate all plant pests (including weeds and invasive alien species, biological control agents, and living modified organisms). Plant pests are defined as "any species, strain or biotype of plant, animal or pathogenic agent injurious to plants or plant products" (Article II of the IPPC). Plant health legislation should include within its remit plants, plant products and other regulated articles (including soil, wood packaging materials and conveyances) that are capable of harbouring plant pests. How these terms are defined in legislation affects the scope of coverage of the law, and the latter has implications on what phytosanitary measures and actions can be taken, who can take the actions, and the commodities covered. Definitions in national law should be aligned with the *International Standards for Phytosanitary Measures (ISPMs) No. 5: Glossary of phytosanitary terms*.

Principles for the application of phytosanitary measures

Legislation should establish phytosanitary measures that are: scientifically justified, based on pest risk analysis, and the least restrictive means of achieving the importing country's appropriate level of phytosanitary protection (ISPM 1: *Phytosanitary principles for the protection of plants and the application of phytosanitary measures in international trade*). Other applicable principles are that phytosanitary measures are necessary to address, and proportional to, the risk. For AMR specifically, and for phytosanitary measures that would

require the use of antimicrobials, this means that risks posed by pests, as well as their treatment with antimicrobials versus alternatives, would be subject to an assessment, management and communication of the risk prior to the adoption of measures.

Responsibilities of the competent authority

Article IV of the IPPC requires each contracting party to establish the competent authority for plant protection (a National Plant Protection Organization (NPPO)), define its structure (including all composite units), and assign the NPPO the following functions:

- conducting pest risk analysis;
- conducting surveillance for plant pests on growing plants, including both areas under cultivation (e.g. fields, plantations, nurseries, gardens, greenhouses and laboratories) and wild flora, and on plants and plant products in storage or in transportation;
- inspection during import and export with the objective of preventing the introduction and spread of pests;
- issuing phytosanitary certificates for exported consignments;
- protection of endangered areas;
- designation and maintenance of pest free areas and areas of low pest prevalence;
- responding to pest outbreaks and phytosanitary emergencies.

The NPPO should be tasked by law to establish a list of regulated pests and to approve control programmes to control such pests. The NPPO should use pest risk analysis as the basis for the design of phytosanitary measures. The NPPO should have a mandate over the entire territory, responsible for plant health over cultivated plants and wild flora (including forest areas).

The inspection corps of the NPPO should be mandated to support the enforcement and implementation of the phytosanitary system. Official laboratories should be designated to carry out the required analysis and diagnostics of samples taken under the law with appropriate provisions for quality control. Laboratories can be public or private, or even outside the country, provided there is official recognition and designation as an official laboratory by law.

Surveillance

Appropriate pest surveillance can help countries determine the occurrence and spread of plant pests, and thereby take measures that will ultimately reduce the need for antimicrobials in plant production overall by targeting pest outbreaks and incursions in a timely manner. Early detection of pests new to an area is a key element of pest eradication or containment programmes. Legislation may impose a general duty on the public to report the (suspected) presence of regulated pests to the NPPO. Areas, places, and sites of production that are officially recognized as pest-free may be maintained through surveillance and monitoring in collaboration with the competent authority (this framework can facilitate the issuance of phytosanitary certificates for exports).

Pest outbreaks and phytosanitary emergencies

The detection of certain types of regulated pests (quarantine pests) during inspections or upon notification by a stakeholder may trigger containment and eradication measures by the NPPO. Legislation may circumscribe such phytosanitary measures (e.g. prohibiting movement of items, prescribing certain treatments or ordering destruction of items). If a need arises, the NPPO should have the power to declare (or recommend to the

responsible minister to declare) a pest outbreak or phytosanitary emergency. Correlated powers should be proportionate, technically justified and time-bound and include setting the limits of the quarantine area and buffer zones, restricting or prohibiting the movement of regulated articles and other measures to control and eradicate the quarantine pest. The administration and logistics necessary to activate, implement and coordinate emergency actions should be outlined in a phytosanitary emergency response plan.

In Norway, the *Regulations related to plants and measures against pests (as amended in 2016)* place obligations on both the plant and plant product businesses as well as the competent authority to prevent the introduction and spread of pests and to control any outbreaks. Certain businesses involved in plant production and marketing are required to be registered with the authority (Section 7) and are obliged to carry out controls (Section 9).

Import and export

Plant health risks from outside the country are controlled through import permits and risk-based inspection schemes as well as transit control. All regulated articles should meet the requirements established by law in order to gain access to the territory, including accompaniment by a phytosanitary certificate (issued by the NPPO of the exporting country, which certifies compliance with the phytosanitary import requirements) where required. The ISPM 20 sets out detailed guidelines for a phytosanitary import regulatory system. The law should prescribe the actions to be taken when an imported consignment does not comply with phytosanitary import requirements (Article VII.1b of the IPPC, and the ISPM 20), notably where regulated pests are detected.

Similarly, for exports, legislation should establish a phytosanitary certification system that ensures exported plants, plant products and other regulated articles are in conformity with the phytosanitary requirements of the importing country (Article V(1) of the IPPC; the ISPM 7). Phytosanitary certificates must use the models set out in the Annex to the IPPC. The NPPOs bear responsibility for the procedures for maintaining the phytosanitary security of the consignment after its certification.

10. Best practices for legislative reform

While the previous Sections focused on technical and *substantive aspects* of reform, this Section provides an overview of the steps and sequencing involved in reforming the national legal frameworks for AMR in the agriculture sector. It encapsulates best practices relating to the *procedure* for reform. It is recognized that each country has its own history, politics, traditions, international obligations, legal system, institutions, agricultural priorities and resources, all of which will affect their choices and strategies for regulating AMR. Furthermore, a country's legislative reform tradition will offer the most applicable guidance on required procedures, including the degree of involvement of specialized agencies to assist in the reform process (such as legal drafters from the agency responsible for preparing and reviewing legislation). A careful analysis of the country context by national lawyers is always advised.

Regulatory Impact Assessment

Regulatory impact assessments (RIAs) can be used to examine different regulatory options to address AMR, including the decision to legislate. This process looks at various options to achieve a particular outcome and provides evidence for the selection of a particular option that yields the most significant net benefit. An RIA should estimate the likely direct and indirect costs of the various options and describe their expected benefits (and who bears such costs and benefits), including the cost of inaction. Consultation allows for a more complete evidence base and is an important part of data collection. The multidisciplinary approach inherent in RIA processes enables an understanding of the various highly multifaceted linkages and connections inherent to AMR and is thus useful in identifying impacts that might otherwise be unforeseen. The RIA process looks at positive and negative effects of proposed and existing regulatory tools as well as non-regulatory options. As RIAs may be resource intensive, developing countries should be selective in RIA application, with processes simplified and only strategically used. Pre-screening checklists can be used to eliminate options that are unfeasible or that may have disproportionate impacts or that are high-risk interventions.

RIA processes typically include: (i) identification of the problem and its context; (ii) determination of the need to regulate and the degree of intervention required; (iii) a collection of relevant data relating to current needs and future needs; (iv) identification of alternatives, including non-regulatory approaches, to resolve the problem; (v) estimation of benefits and costs of the different options; (vi) selection of the best option with justifications for selection; (vii) recommendation of options and strategies for implementation including risk mitigation; (viii) an identification of monitoring and evaluation strategies for the option selected (OECD, 2020). Consultations with stakeholders and experts should take place throughout the process.

An RIA often brings up the direct and indirect costs and benefits of certain challenges and interventions. It is thus a useful tool to explore aspects that may otherwise not be a primary consideration, such as gender dimensions, in preventing AMR. This would be the case, for instance, in countries where women have an important role in livestock management, including the use of VMPs. A gender and equity focus should be adopted when revising the legislation, and this means examining AMR patterns, pathways and key drivers from a gender perspective as well as other social aspects (e.g. occupation, income, age, geographic location, education level, etc.) (WHO, 2018). This provides valuable information on whether some groups are affected differently, offering the government deeper insights for more effective legislative solutions (WHO, 2018).

The questions outlined in Box 10 may guide preliminary discussions about the most effective means to address AMR regulatory challenges.

Box 10. Guiding country-level analyses

- What antimicrobial resistance (AMR)-related policy measures would be most effective to address AMR and antimicrobial stewardship in the country?
- Do these policy measures take into consideration all AMR-relevant sectors?
- Would these measures require legal underpinning? Would these measures require intersectoral legislation or sector-specific legislation?
- Which measures may be better addressed through non-legislative means (manuals/codes of practice or awareness-raising campaigns)?
- What are the challenges to effectively incorporating the required elements or mechanisms into legislation?
- Has the country undertaken a feasibility and impact analysis of the considered regulatory measures?

  More specifically, can the identified legal reform be: (a) implemented; and (b) enforced? Is it technically feasible? Is it legally feasible? Is it practical? Is it sustainable? What are the resources (technical, human, financial) available for the regulatory option? What is the best locus for the specific intervention (national, local, sectoral/coordinated, etc.)?

Legislative analysis for reforms

Any legal reform process for AMR should begin by identifying the country-specific regulatory challenges and needs, to ensure the effective implementation of the National Action Plan. These may include regulatory needs that would require the involvement of more than one ministry, such as the establishment of an AMR governance mechanism. Sector-specific regulatory reforms may also be warranted, that aim to: (i) strengthen the regulation of antimicrobials (medicines, VMPs, pesticides, medicated feed); (ii) prevent contamination of food and the environment with antimicrobial residues and antimicrobial-resistant microorganisms; or (iii) improve animal and plant health and resilience to disease, thus minimizing the use of antimicrobials.

The need for legislative reform might only be identified during NAP implementation, at the moment of setting up a multi-sectoral policy initiative (such as a common framework for integrated surveillance), or by the line ministries seeking to incorporate international reference standards in sector-specific laws. All of these initiatives should be underpinned by a One Health approach (see Section 1.2 of this Study).

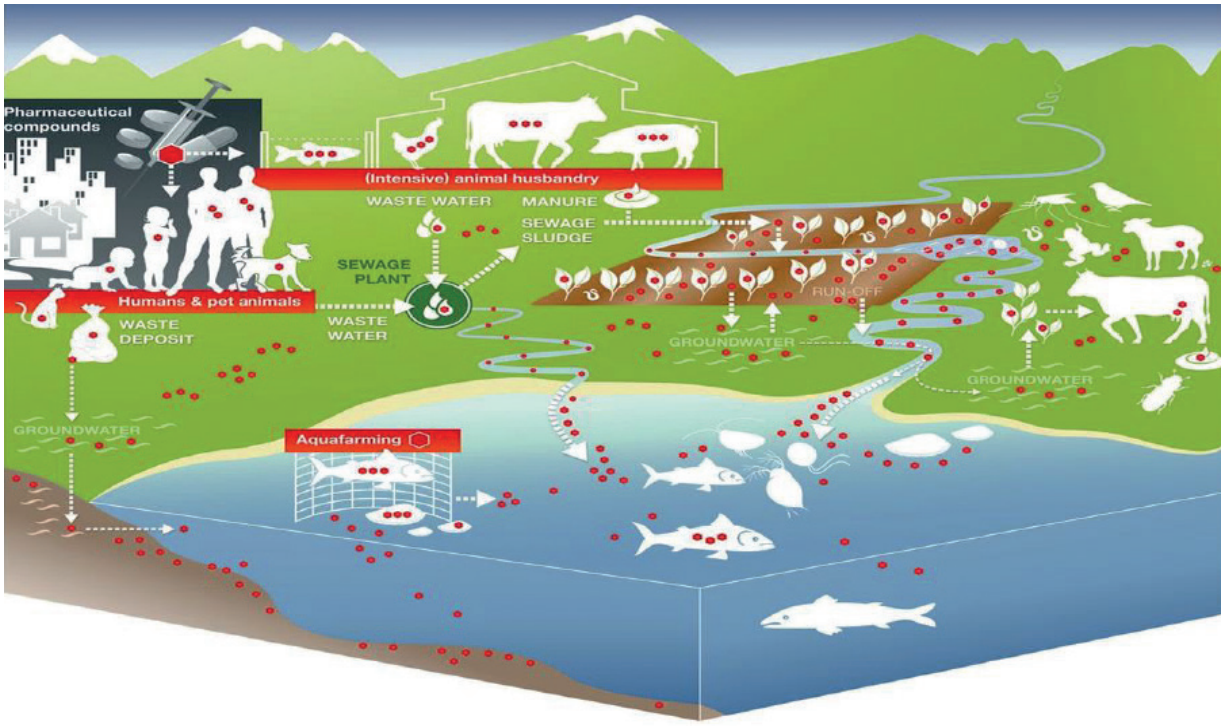
International legally binding obligations as well as the reference standards, recommendations and guidelines of internationally recognized entities will serve as a basis for evaluating national legislation. The resulting gap assessment will identify opportunities for legal reform. Stakeholder consultations are important at various junctures and will enable the tailoring of international standards and guidelines to the specific needs and context of the country.

The following points set out the sequence of steps to analyse the effectiveness of the national legal framework to respond to AMR.

1. Identify national AMR priorities

- National priorities on AMR may be embedded in the National Action Plan, in AMR- or sector-specific policy documents and strategies, or may be derived from stakeholder consultations

Figure 1. Antimicrobial dispersal into water bodies and the environment



Note: Antimicrobial usage in humans, animals and agriculture, and resulting dispersion of antimicrobial residues into aquatic and terrestrial environments.

Source: Berkner, S., Konradi, S., & Schönfeld, J. 2014. *Antibiotic resistance and the environment-there and back again: Science & Society series on Science and Drugs*. EMBO reports, 15(7), 5 pp. https://doi.org/10.15252/embr.201438978

2. Identify legally binding international obligations, as well as recommended practices included in standards, guidelines and other non legally binding (soft law) instruments

- Depending on the country's commitments, binding agreements might include obligations in any of the instruments discussed in Section 3 of this Study. Regional and bilateral agreements may also incorporate binding obligations that might be either AMR- or sector-specific.
- International soft-law instruments would include, among others, the standards approved by the Commission of the *Codex Alimentarius*, the WOAH *Codes on Terrestrial and Aquatic Animal Health* or the FAO/WHO *International Code of Conduct on Pesticide Management*.
- Relevant publications by FAO and partner Quadripartite organizations also provide authoritative, expert guidance, such as *The FAO Action Plan on Antimicrobial Resistance 2021-2025* and the *WHO Global Benchmarking Tool (GBT) for Evaluation of National Regulatory System of Medical Products* (WHO, 2021) specific to medicines and the public health sector.

3. Collect and analyse legislation and identify sector-specific regulatory needs

- Following an inventory of the national legal framework (primary and secondary legislation across the different sectors as well as federal and decentralized instruments where these exist), an analysis or assessment of these texts against international reference standards would follow. The analysis should identify legal gaps and opportunities for legal reform. Such an analysis should take into consideration:

- **The national constitution and legal instruments that describe the constitutional arrangements of the state:**
  - Identify the allocation of powers between different levels of government; determine the subject matters legislated at pre-defined levels of government; and ascertain the way in which international obligations are given effect in the national legal framework.
- **Legislation that regulates antimicrobials (see Section 7 of this Study)**
  - *veterinary medicinal products;*
  - *pesticide legislation;*
  - *feed legislation; and*
  - *other substances with antimicrobial effects.*
- **Legislation that prevents contamination of food, water and the environment with antimicrobials and antimicrobial residues (see Section 8 of this Study)**
  - *food safety legislation; and*
  - *environment legislation, including water, soil and waste management.*
- **Legislation that helps minimize the need for antimicrobials (see Section 9 of this Study)**
  - *animal health, production and welfare legislation.*
  - *plant protection legislation; and*
  - *legislation that governs veterinary professionals and encourages prudent use of antimicrobials.*

- The analysis of the legal framework may comprise all the foregoing sectors (including public health) with a view of undertaking a genuine One Health approach, or the assessment may focus on one specific sector. Regardless, even a sector specific analysis would likely need to take into consideration several of the above-mentioned legal areas in order to provide a comprehensive review. For instance, an analysis that focuses on VMP legislation would require at minimum an examination of legislation on (human) medicines, the environment, feed, veterinary professionals, and animal health.

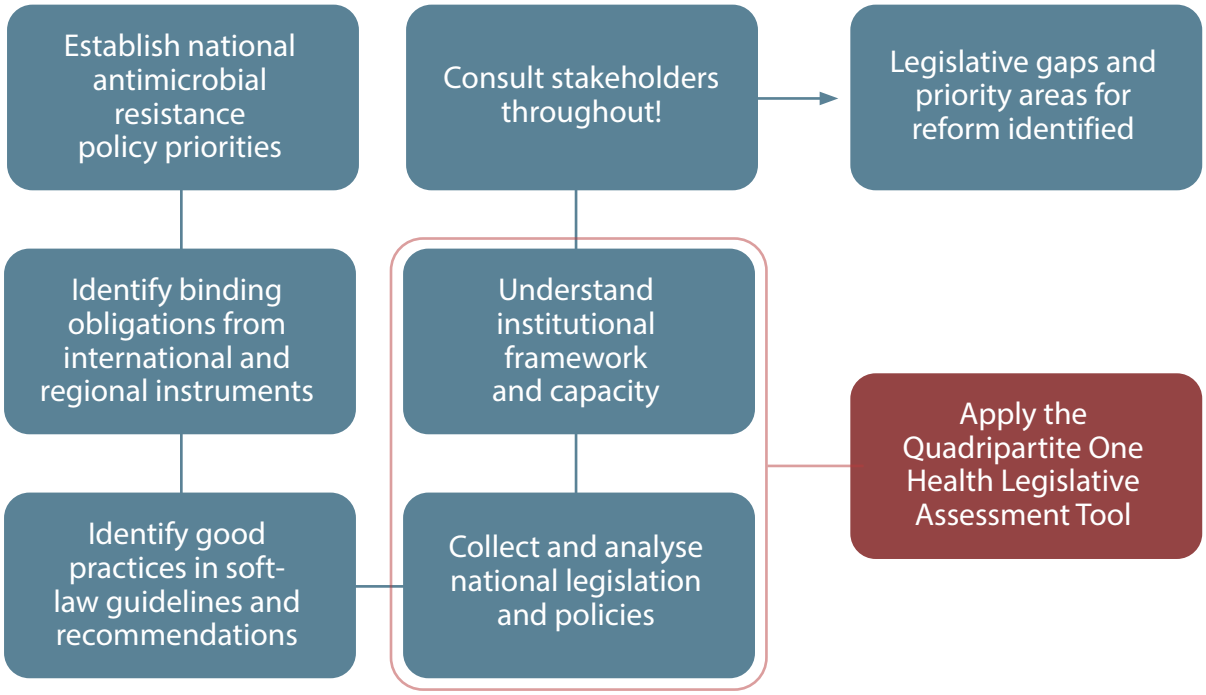
- The legislative analysis will yield insights into the institutional structure for the different areas relevant for AMR, and into the structures aimed at coordination across sectors. This double-pronged legal and institutional analysis should encompass the many institutions within the country that have a role to play in addressing AMR in their domain, including at least those responsible for human and veterinary medicine, agriculture, finance and the environment, as well as the existing coordination mechanisms across ministries and other entities. The institutional analysis should reveal whether:
  - regulators are aware of the scope of their obligations;
  - the appropriate authority has been empowered sufficiently by law to deal with and enforce matters within its mandate;
  - there are overlaps in responsibility among different authorities; and
  - cooperation among different institutions function as designed by the law.

- A preliminary assessment of the actual implementation of the legislation is important. The available resources, both human and other types, should also be assessed to understand the overall capacity for the country to implement the relevant provisions of law. Regulators should avoid creating

expensive or complicated tasks for the relevant institutions and overly burdensome obligations for the private sector. In many countries, there is a significant difference between what is in the statute books and what regulators actually do (or not) in governing a particular area. Unless regulators look at any problems relating to enforcement, implementation, and compliance, any of the reasons that have hampered the success of current legislation are likely to continue under a new framework. Implementation issues are often the result of the development of unrealistic legislation that does not pay attention to the country's actual monitoring and enforcement capacities, and that does not sufficiently engage and respond to private sector needs. A regulatory reform process should be predicated on what the country can realistically put in place, and that actively engages all stakeholders from the early stages of the process. Understanding how legislation is de facto implemented may require joint legal and technical assessments and requires stakeholder consultation. Along the same lines, regulators may also want to use any modified variant of *ex-ante* or ex-*post* regulatory impact assessment (RIA) to assess the likely positive and negative impacts of different regulatory options that can be taken (and also the cost of inaction).

- The understanding of the factual situation and the legislative framework would allow the government to decide: (i) whether any *new* regulatory measures are required; (ii) whether small adjustments or *amendments* may be appropriate; or (iii) whether *improved and strengthened implementation* of existing legal instruments and requirements would be enough to address the gaps that have been identified.

Figure 2. Steps to understand the legal framework for antimicrobial resistance in the food and agriculture sectors



4. Options for regulatory reform

The choice of legal instrument would depend on the nature and content of the proposed legislation and is influenced by the national legal system and legislative drafting tradition. The instrument to implement reforms may vary from primary legislation to implementing regulations or may be a Memorandum of Understanding among ministries. There may be a need for revision of texts beyond the targeted sector

to include reform of other legislation relevant to AMR; this would align with a One Health approach. Appendix 1 offers an example of the range of European Union actions to address AMR (and the supporting legal instruments for such actions) that illustrate the multisectoral responses that have been taken in the region.

Regulatory reform for AMR frameworks is a multidisciplinary exercise that calls for the input of lawyers, veterinarians, plant and food scientists, environmental experts, economists, and other specialized fields of expertise. If new legislation is needed (or if amendments are required), such reform should be undertaken in a participatory and inclusive manner with wide-ranging stakeholder consultations. The key stakeholders that should be consulted include (at minimum): agricultural and animal producers and their associations; civil society organizations; food and feed industry stakeholders; food traders; pharmaceutical companies; and veterinarian associations. This approach helps better adapt and incorporate international reference standards and best practices to the individual country's context, including the interests and needs of stakeholders. Sharing information in this manner also serves the purpose of awareness-building on AMR. Broad stakeholder consultation facilitates consensus-building and paves the way for the implementation of the new legislation; stakeholders feel a sense of ownership of the proposed regulatory changes.

Finally, in designing control frameworks to regulate antimicrobial-related activities, regulators should be aware that it is possible to use differentiated requirements to distinguish between the needs, risk and activities associated with small versus large operators, without lowering safety standards. Stakeholder consultations will enable achievement of consensus on the way forward. Smaller retail shops and stalls may benefit from certain basic and simplified requirements for authorization while large importers, distributors, manufacturers, and producers would be subject to more rigorous authorization processes. All operators should be required to follow rules on aspects such as packaging and labelling, but perhaps smaller operators would not be subject to rigorous record-keeping duties. These considerations depend on the realities of the operators in a given country. The threshold to distinguish the various categories of operators can be based on size or trading volumes, annual income, or other distinguishing factors.

Regulators may use the *Quadripartite One Health Legislative Assessment Tool for Antimicrobial Resistance* which is a specially designed tool that is closely aligned with the approach taken in this Study (see Box 11).

Box 11. Quardipartite One Health Legislative Assessment Tool for antimicrobial resistance

The *Quardipartite One Health Legislative Assessment Tool for antimicrobial resistance* provides guidance on how to assess national legislation relevant for addressing antimicrobial resistance (AMR). It assists in the identification of gaps in the legislative framework and enables prioritization of potential solutions (regulatory options) to address them. This Tool is funded by the Multi-Partner Trust Fund and developed by the Food and Agriculture Organization of the United Nations (FAO), the World Health Organization (WHO) and the World Organisation for Animal Health (WOAH), with the collaboration of the United Nations Environment Programme (UNEP). As an instrument that can be used by countries in all regions in the fight against AMR, the Tool is aligned with the W HO *Global Action Plan on antimicrobial resistance*.

Source: FAO, FAO, UNEP, WHO & WOAH. (forthcoming). *One Health Legislative Assessment tool for AMR.*

Enforcement

Countries may find that their regulatory frameworks are adequate, but they face significant challenges in enforcing existing rules and regulations. Having a well-designed legal framework is of limited use without the ability to enforce its provisions in practice. The NAPs established in many countries recognize the need for improved enforcement to better implement legislative rules and mechanisms that are already in

place. The *Eritrean National Action Plan on antimicrobial resistance 2021–2025* identifies "an urgent need to enforce the existing laws to curtail the dispensing of drugs by non-professionals, peddling of medicines and pesticides and the illegal purchase of antimicrobials by farmers" (State of Eritrea, 2021, p. 14). Similarly, the *Multi-Sectoral Action Plan on Antimicrobial Resistance in Cambodia 2019-2023* lists as one of its "important findings" as the "Need to enforce regulations and rational use of antibiotics in agriculture and human healthcare" (Kingdom of Cambodia, 2019, p. ii).

Box 12 presents an outline of some common legal tools for enforcement. Countries should examine which of the highlighted tools work well in their jurisdictions. Where a certain enforcement tool presents challenges for implementation, these problems should first be addressed. Such matters may exceed sector-specific implementation and may be a broader problem of governance, rule of law and enforcement of legislation in the country. In such cases, the coordination mechanism (where it exists) could be a useful vehicle through which to bring in broader stakeholders (such as the government entities responsible for administrative law and justice, and law enforcement), in order to strengthen the ways in which enforcement provisions can be effectively implemented.

Box 12. Tools for enforcement

Competent authorities should be granted the power to intervene through various tools and mechanisms. These tools may be found in sector legislation, or in criminal, civil or administrative or procedural legislation. While many enforcement mechanisms are procedural in nature, it is important for transparency, to prevent abuses of power, and to safeguard public rights, that these tools are placed in higher-level legislation that is subject to rigorous scrutiny during approval.

Powers

Inspectors may have varying degrees of power ascribed to them under different sectoral laws. Depending on the jurisdiction, common powers established under primary legislation for inspections include the powers to: (i) access premises and vehicles/vessels; (ii) request and access documents; (iii) take samples; (vi) order treatments, disinfection, disinfestation or other measures; and (v) order application of specific measures including: seizure or destruction of regulated items; prohibit cultivation or moving of regulated items; stop distribution of products that do not meet legal requirements, and confiscate illegal items; and suspend or close facilities (or parts of activities at a facility). Some sectoral laws, such as animal health legislation, may contain more significant powers for inspectors, such as the killing of diseased animals, stopping movement of animals and vehicles, and other emergency actions. The powers of inspectors should be adequately robust to enable them to effectively carry out their duties without fear of intimidation or reprisal (including support from other law enforcement officials such as the police and local authorities), and this includes the duty of cooperation of those subject to an inspection or investigation. These powers must nevertheless be clearly circumscribed to limit opportunities for abuse of authority. Operators or other parties subject to inspections or who have had penalties imposed on them should be granted a mechanism to appeal to third parties to contest actions or decisions taken by the competent authority.

Procedures

Legislation should provide procedural and legal guarantees, as well as clarity over which objects inspectors may have significant powers. These rules should be buttressed in regulations, inspection manuals and standard operating procedures, to enable uniform implementation throughout the country and to ensure that proper protocol is followed during inspections and investigations.

Breaches, liabilities and offences

An action or omission that constitutes a breach, liability or offence should be clearly stated in the legal framework, and a corresponding penalty should be prescribed.

Box 12. Tools for enforcement (cont.)

Penalties

Penalties may be administrative, civil or criminal, depending on the categorization of the offence and the severity or significance of its impact. These penalties can be applied individually or in any combination. Legislation should indicate a maximum applicable penalty for a given offence. Article 3.4.4 of the WOAH *Terrestrial Animal Health Code* (applicable to legislation in the veterinary domain) states that penalties and sanctions should be imposed according to existing penal procedures and administrative sanctions that are designed for immediate application in the case of activities posing a risk to animal health, animal welfare or public health.

Administrative (or civil) penalties may take many forms, which include fines, suspension or revocation of approvals, permits, licences, etc., and forfeiture of regulated articles, etc. Administrative penalties can be cost-effective, timely and practical. Such penalties can be imposed by the competent authority and do not necessarily require involvement of the courts unless the penalty is contested.

Civil penalties are often imposed as judgements for restitution following a legal hearing before an adjudicating body. Often the penalty is in the form of fines or damages. For example, a person or entity may be required to pay a financial amount in order to remedy the damage to persons or the environment, as a result of illegal dumping of waste, which may also include the cost of clean-up. Costs associated with liabilities relating to the environment can be significant. This mechanism is used to compensate for harm that is already done.

Criminal penalties are used to punish wrongful conduct either through fines or imprisonment (or both) and are imposed following a hearing before an adjudicating body in line with the criminal procedure and legislation of the country.

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Appendix 1. Range of European Union initiatives to address antimicrobial resistance and supporting regulatory instruments

International instruments (non-binding)

This Appendix outlines the range of initiatives within a (regional) jurisdiction to illustrate a multisectoral approach to antimicrobial resistance (AMR). The response to AMR in the European Union is addressed under the framework of *A European One Health Action Plan against Antimicrobial Resistance* and covers many of the themes discussed in the Study. The progress report issued as part of the Action Plan comprehensively covers European Union AMR-related activities, including regulatory actions (European Commission, 2023). This Appendix highlights key actions taken in the European Union to address AMR and lists the corresponding legal instruments for so doing, adhering to the presentation and numbering used in the progress report for facilitated cross-referencing.

INITIATIVES	RELATED LEGAL INSTRUMENTS
1.1 Better evidence and awareness of the challenges of AMR	
Review European Union implementing legislation on monitoring AMR in zoonotic and commensal bacteria in farm animals and food.	*Commission Implementing Decision (EU) 2020/1729 of 17 November 2020 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria.*
Review European Union implementing legislation on reporting communicable diseases in humans.	*Commission Implementing Decision (EU) 2018/945 of 22 June 2018 on the communicable diseases and related special health issues to be covered by epidemiological surveillance as well as relevant case definitions.*
Identify and assess under the Animal Health Law, resistant bacteria that cause transmissible animal diseases and, if necessary, develop harmonized rules for their surveillance.	*Regulation (EU) 2016/429 of the European Parliament and of the Council of 9 March 2016 on transmissible animal diseases.*
1.2 Better coordination and implementation of European Union rules to tackle AMR	
Stepping up EU actions to combat antimicrobial resistance in a One Health approach. Encourage Member States to implement One Health National Action Plans for coordinated AMR response. Improve comparable and compatible data and information collection on AMR and antimicrobial consumption (AMC) at all levels. Develop integrated surveillance and monitoring systems for AMR and AMC. Sharing data and information across sectors for a more effective and coordinated response to AMR. Ensur full and effective implementation of One Health AMR policies and actions through Member States cross-sectoral cooperation and stakeholders' involvement, particularly through the EU AMR One Health Network.	*Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach 2023/C 220/01*

INITIATIVES	RELATED LEGAL INSTRUMENTS
Forthcoming veterinary medicinal products and medicated feed Regulations containing concrete restrictions for the prophylactic and metaphylactic use of antimicrobials. Moreover, work towards European Union implementing and delegated acts established in these Regulations including a list of antimicrobials reserved for human use, drawing up a list of antimicrobials that cannot be used under "cascade use", limits for residues of antimicrobials in feed, requirements for animals or products of animal origin exported from third countries and methods for data gathering and reporting on the sales and use of antimicrobials.	*Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products.* *Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed.*
Develop European Union guidelines for the prudent use of antimicrobials in human medicine. Guidelines for the prudent use of antimicrobials in veterinary medicine assist Member States to implement European Union guidelines for the prudent use of antimicrobials in veterinary medicine.	*Commission notice – EU Guidelines for the prudent use of antimicrobials in human health (C/2017/4326)* *Commission notice – Guidelines for the prudent use of antimicrobials in veterinary medicine* *(2015/C 299/04*
1.4. Better addressing the role of the environment	
Adopt a European Union strategic approach to pharmaceuticals in the environment.	*Communication from the Commission to the European Parliament, the Council and the European Economic and Social Committee: European Union Strategic Approach to Pharmaceuticals in the Environment. COM(2019) 128 final.*
1.5. A stronger partnership against AMR and better availability of antimicrobials	
Work with stakeholders to ensure the availability of human and veterinary antimicrobials and continued access to established products; provide incentives to increase the uptake of diagnostics, antimicrobial alternatives and vaccines.	*Regulation (EU) 2017/746 of the European Parliament and of the Council* *of 5 April 2017 on* in vitro *diagnostic medical devices.*
2.5. Develop new economic models and incentives	
Analyse European Union regulatory tools and incentives – in particular legislation for orphan medicinal products and medicinal products for paediatric use – to use them for novel antimicrobials and innovative alternative medicinal products that currently do not generate sufficient returns on investment.	*Regulation (EC) No 141/2000 of the European Parliament and of the council of 16 December 1999 on orphan medicinal products.* *Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.*

INITIATIVES	RELATED LEGAL INSTRUMENTS
3.1. A stronger European Union global presence	
Boost support for the International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH), and the International Conference on the Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) on relevant international guidelines/standards/norms related to AMR.	United Nations *Political Declaration of the High-level Meeting on Universal Health Coverage "Universal health coverage: moving together to build a healthier world"*
Look for synergies with the United Nations Strategic Approach to International Chemicals Management's work on the emerging policy issue of pharmaceuticals in the environment.	*Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions – Chemicals Strategy for Sustainability Towards a Toxic-Free Environment. COM(2020) 667 Final.*
Promote international regulatory convergence between the European Medicines Agency (EMA) and other regulatory agencies such as the United States Food and Drug Administration (FDA) and the Japan Pharmaceuticals and Medical Devices Agency (PMDA) on development plans for new promising antimicrobials.	
3.2. Stronger bilateral partnerships for stronger cooperation	
Advocate European Union standards and measures for tackling AMR in trade agreements and incorporate them into cooperative arrangements in trade agreements.	*Free Trade Agreements* under negotiation with Indonesia, Australia and New Zealand contain articles on antibiotic resistance.

Antimicrobial resistance (AMR) is a global challenge with detrimental impacts on human, animal, plant, and environmental health. The use of antimicrobials is critical for the treatment of infectious diseases and pests in humans, animals (both aquatic and terrestrial) and plants. However, the inappropriate and excessive use of antimicrobials in human health systems and in the food and agriculture sectors has exacerbated AMR, which refers to the inherited or acquired characteristic of microorganisms to survive or proliferate in concentrations of an antimicrobial that would otherwise kill or inhibit them. Therefore, AMR in food and agriculture poses risks to food systems, livelihoods and economies.

Recognizing the multifaceted causes and impacts of AMR, as well as developing appropriate regulatory solutions, requires a multisectoral 'One Health' response that spans a range of sectors (including human health, the veterinary domain, agricultural production, and the environment, among others), as well as action at local, national and global levels. The breadth of regulatory areas involved, and the rapidly evolving scientific developments that update the evidence base for policymaking, render the AMR issue a considerable regulatory challenge.

This Legislative Study is designed to demonstrate the various ways in which key AMR risks and challenges can be tackled through legislation. It outlines the concepts and mechanisms relevant to address AMR for the twin goals of attaining responsible and producent use of antimicrobials and the mitigation of AMR. As such, it aims to respond to the UN General Assembly's call for "strengthening of regulatory capacity" as well as efforts to "increase awareness and knowledge, and [share] good practices and findings" in the global fight against AMR.

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