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International instruments on the use of antimicrobials across the human, animal and plant sectors

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Contents

List of figures, tables and boxes

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List of abbreviations

ADI	acceptable daily intake
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AMR	antimicrobial resistance
AMU	antimicrobial use
API	active pharmaceutical ingredient
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
CIA	critically important antibiotic
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EIA	environmental impact assessment
EML	essential medicines list
FAO	Food and Agriculture Organization of the United Nations
FAO GBS	FAO Governing and Statutory Bodies
FIP	International Pharmaceutical Federation
GHS	Globally Harmonized System of Classification and Labelling of Chemicals
GMP	good manufacturing practices
GRP	good regulatory practices
IACG	Interagency Coordination Group
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICoCPM	International Code of Conduct on Pesticide Management
IPC	infection prevention and control
IPPC	International Plant Protection Convention
MDR	multidrug-resistant
MRL	maximum residue limit
OIE	World Organisation for Animal Health
PAH	polycyclic aromatic hydrocarbon
RMR	risk management recommendation
SPS	Sanitary and Phytosanitary
TB	tuberculosis
TBT	Technical Barriers to Trade
TFAF	Task Force on Animal Feeding
UN	United Nations
UNECE	United Nations Economic Commission for Europe
UNEP	United Nations Environment Programme
VICH	Veterinary International Conference on Harmonization (in full: International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products)
VMP	veterinary medical product
WAHID	OIE World Animal Health Information Database
WHA	World Health Assembly
WHO	World Health Organization
WHOLIS	World Health Organization Library Database
WTO	World Trade Organization

Introduction

This compilation provides an overview and analysis of international instruments that provide standards related to the use of antimicrobials. The purpose of the compilation is to identify existing instruments and standards in order to guide both their implementation and to inform discussions and direction for future international instruments related to antimicrobial use.

1.1 Objective

The objectives of this compilation[1] are as follows:

1. to identify existing *international instruments that provide standards related to antimicrobial use* across the human, animal and plant sectors, including ensuring food safety and preventing release of antimicrobials into the environment;
2. to identify areas where there are *gaps and/or opportunities* in the current international guidance and regulations; and
3. to identify existing frameworks for the *monitoring of implementation* of these instruments.

The compilation covers only instruments related to the use of antimicrobials and thus does not include international standards in other important areas relevant for antimicrobial resistance (AMR), such as infection, prevention and control (IPC) or the improvement of animal health status.

1.2 Background

In 2015, the Sixty-eighth World Health Assembly (WHA) adopted the Global Action Plan on Antimicrobial Resistance developed by WHO in collaboration with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE).[2] Affirming the urgent need for cross-sectoral action to address AMR, the assemblies of FAO[3] and the OIE[4] also adopted resolutions

1 For the purpose of this document: Antimicrobials consist of antibiotics, antifungals, antivirals and anti-parasitic agents. Resistance development to all of these medicines is what is known as antimicrobial resistance, whereas resistance development in bacteria only is known as antibiotic resistance. Because of the separate public health responses for antivirals and anti-parasitic agents in human health – for instance for HIV and malaria, respectively – this report focuses on antibiotic and antifungal resistance only.

2 Resolution WHA68.7. Global action plan on antimicrobial resistance. In: Sixty-eighth World Health Assembly, Geneva, 18–26 May 2015. Resolutions and decisions, annexes. Geneva: World Health Organization; 2015 (https://apps.who.int/gb/ebwha/pdf_files/WHA68-REC1/A68_R1_REC1-en.pdf#page=27, accessed 20 June 2020).

3 Resolution 4/2015. Antimicrobial resistance. In: FAO Conference, 39th Session, Rome, 6–13 June 2015. Rome: Food and Agriculture Organization of the United Nations; 2015 (http://www.fao.org/3/a-mo153e.pdf, accessed 20 June 2020).

4 Resolution No. 26. Combating antimicrobial resistance and promoting the prudent use of antimicrobial agents in animals. In: Resolutions adopted by the World Assembly of OIE Delegates, 83rd General Session, 25–29 May 2015. Paris: World Organisation for Animal Health; 2015 (https://www.oie.int/fileadmin/Home/eng/About_us/docs/pdf/Session/A_RESO_2015_public.pdf, accessed 20 June 2020).

supporting the Global Action Plan in 2015. The Global Action Plan proposes interventions to control AMR, including optimizing the use of antimicrobials in humans and in animals and taking a One Health approach.

The World Health Assembly also requested the Director-General of WHO to work towards developing a global development and stewardship framework to combat AMR, in consultation with Member States and relevant partners. The aim of the framework was "to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries and in line with the Global Action Plan on Antimicrobial Resistance".[1]

During the Sixty-ninth World Health Assembly in May 2016, the Director-General presented WHO Member States with a number of options for such a framework on AMR (documents A69/24 and A69/24 Add. 1). Later that year, in September 2016, the United Nations General Assembly, in its Political Declaration of the High-Level Meeting on AMR, called upon the Tripartite organizations – FAO, the OIE and WHO – to "finalize a global development and stewardship framework, as requested by the World Health Assembly".[5]

In response to this request, the Tripartite held two consultations. First, on 9–10 November 2017, the Tripartite held an informal consultation on a roadmap with members, relevant international organizations and non-state actors during which a concept for the overarching framework was presented and discussed.[6] Second, on 1–2 October 2018, the Tripartite, in collaboration with UNEP, held a second consultation with members, relevant international organizations and non-state actors to discuss the form, structure, content and possible goals for a framework.[7]

In the 2019 report to the Secretary-General of the United Nations, the Interagency Coordination Group (IACG) on AMR called on the Tripartite and UNEP "to expedite [the framework's] development in line with the scope described in the 2015 World Health Assembly resolution on antimicrobial resistance".[8] In its Memorandum of Understanding of 2018, the Tripartite set itself the objective of "[p]repar[ing] a Voluntary Code of Conduct to reinforce implementation of international standards on responsible and prudent use of antimicrobials". During the Seventy-second World Health Assembly in 2019, Member States adopted resolution WHA72.5, which requested the Director-General of WHO to adjust the process and scope of the global development and stewardship framework to combat AMR, considering the recommendations of the IACG.

Based on these mandates and decisions, in November 2019 the Tripartite agreed to develop a compilation of international instruments on the responsible and prudent use of antimicrobials across the human, animal and plant sectors, including relevant environmental instruments.

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5 A/71/L.2. Political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. In: UNGA 71st Session, 21 September 2016. New York: United Nations; 2016 (https://digitallibrary.un.org/record/842813?ln=en, accessed 20 June 2020).

6 Global framework for development and stewardship to combat antimicrobial resistance: draft roadmap. Geneva: World Health Organization; 2017 (http://www.who.int/phi/implementation/research/Roadmap-Global-Framework-for-Development-Stewardship-to-combatAMR_2017_11_01.pdf?ua=1, accessed 20 June 2020).

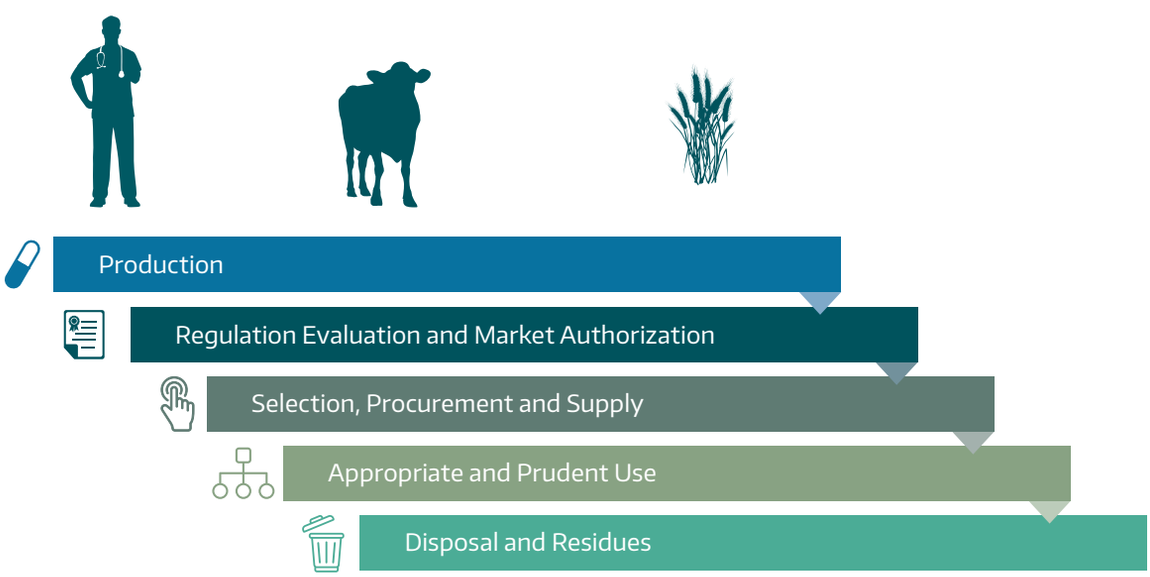
7 Global framework for development and stewardship to combat antimicrobial resistance: draft. Geneva: World Health Organization; 2018 (https://www.who.int/phi/news/WHO_OIE_FAO_UNEP_Working_paper_of_the_framework_FINAL.pdf, accessed 20 June 2020).

8 Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations. Geneva: World Health Organization; 2019. (https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/, accessed 20 June 2020).

2 Scope and methodology

This compilation includes all international instruments related to the use of antimicrobials in the human, animal and plant sectors, including relevant environmental instruments. A broad understanding of "use" is used that includes any emission or release into the environment. The compilation is structured around the life cycle of antimicrobials: from production to marketing authorization and regulatory approval; to selection, procurement and supply; to responsible and prudent use; and ultimately disposal by the end user (Fig. 1). The instruments related to the environment are included throughout this life cycle as regulation of the use of antimicrobials and any related emissions of antimicrobials into the environment can occur at different stages of the life cycle, from spillage into the environment during the production process to the disposal of expired products and related waste and wastewater.

Fig. 1. The antimicrobial life cycle: the series of stages through which antimicrobials pass, from production to disposal by the end user



2.1 Scope

Instruments were either included or excluded from the compilation based on the four criteria listed below (and summarized in Table 1).

Table 1. Summary overview of instruments included and excluded from this compilation

Included	Excluded
■ International instruments providing standards related to use of antimicrobials in the human health, animal and plant sectors ■ International instruments addressing the use of antimicrobials and their release into the environment	■ National and regional instruments related to antimicrobial use ■ Resolutions, declarations and plans or other documents that do not provide standards ■ Instruments from before 2000 that have not been updated since

(1) Substantive scope: The objective of the compilation is to provide an overview and analysis of the existing instruments related to antimicrobial use. It includes/excludes the following instruments:

Included:

- existing international instruments on the use of antimicrobials across the human health, animal and plant sectors;
- international instruments covering pharmaceutical products or chemicals across the human, animal and plant sectors (Tables 2–4) that do not specifically mention antimicrobials but directly influence their use; and
- instruments that address the potential release of antimicrobials into the environment or that otherwise directly influence their release into the environment (Table 5).

Excluded:

- broader AMR relevant instruments not related to the product life cycle, for example, instruments covering IPC, animal and plant health, or behavioural change.

(2) Types of instruments: Instruments that contain standards for governments or other actors are included. These include international guidelines that have been adopted by public entities through formal processes if they provide standards (understood as clear instructions/ guidance on the use of antimicrobials). The compilation excludes resolutions, declarations, (action) plans or other documents that only state intentions or objectives and that do not contain implementable standards. International standards adopted by private entities and business associations are also excluded.

(3) Geographical scope: This compilation only includes multilateral international instruments providing standards for countries or other actions that have been agreed by more than two countries in different regions. National and regional instruments, as well as bilateral agreements, are excluded.

(4) Time frame: Instruments developed or updated in or after the year 2000 are included.

The complete list of international instruments can be found in Annexes I, II and III.

2.2 Methodology

Collection of existing instruments: The Tripartite organizations undertook a review of the existing instruments from November 2019 to June 2020. The initial search examined instruments from organizations that play a leading international role in managing AMR, particularly the OIE, FAO, UNEP and WHO. Subsequently, a search of references to other documents in the preambular text of regulations was undertaken. Furthermore, various databases were searched according to the following search terms: "antibiotic", "antibacterial", "antifungal", "antimicrobial", "antibiotic agent", "antifungal agent", "antimicrobial agent", "antibiotic use", "antifungal use", "antimicrobial use", "antibiotic resistance", "antifungal resistance" and "antimicrobial resistance". Instruments including more general terms related to antimicrobials, such as "pharmaceuticals", "medicines" or "chemicals", were also taken into consideration.

The databases searched included the WHO Library database (WHOLIS), the World Health Assembly and Executive Board repositories, the FAO Governing and Statutory Bodies (FAO GSB) website, the FAOLEX database, ECOLEX, the OIE World Animal Health Information Database (WAHID), the United Nations Official Document System and the International Labour Organization (ILO) Library. The websites of the WHO, FAO and UNEP were also analysed.

Verification process: Following the search process, the list of instruments was reviewed by Tripartite experts at FAO, the OIE, WHO and by UNEP (see Acknowledgements).

3 Compilation of instruments on antimicrobial use

The compilation of instruments (based on Annex I, II and II) was separated into the human health, animal and plant sectors and classified and analysed following the stages of the antimicrobial life cycle (Fig. 1).

3.1 Overview and analysis of instruments on human use

Table 2. Overview of instruments related to human use of antimicrobials across the antimicrobial life cycle

Area	Overview of instruments
Production	■ ICH Q7 *Good manufacturing practice guide for active pharmaceutical ingredients (2000)* / WHO *Good manufacturing practices for active pharmaceutical ingredients* (Annex 2, WHO Technical Report Series, No. 957) (2010) (adopts the ICH Q7 above and is identical) ■ ICH Q10 *Pharmaceutical quality system (2008)* ■ WHO *Good manufacturing practices for pharmaceutical products containing hazardous substances* (Annex 3, WHO Technical Report Series, No. 957) (2010) ■ WHO *Guidance on good practices for pharmaceutical quality control laboratories* (Annex 1, WHO Technical Report Series, No. 957) (2010) ■ WHO *Guidelines on quality risk management* (Annex 2, WHO Technical Report Series, No. 981) (2013) ■ WHO *Good manufacturing practices for pharmaceutical products: main principles* (Annex 2, WHO Technical Report Series, No. 986) (2014) ■ WHO *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance* (Annex 6, WHO Technical Report Series, No. 1025) (2020)
Market authorization and regulatory approval	■ WHO *Guidelines on packaging for pharmaceutical products* (Annex 9, WHO Technical Report Series, No. 902) (2002) ■ WHO *Guidelines for registration of fixed-dose combination medicinal products* (Annex 5, WHO Technical Report Series, No. 929) (2005) ■ WHO *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory authorities (NMRAs)* (2nd edition) (2011) ■ WHO *General guidance on variations to multisource pharmaceutical products* (Annex 10, WHO Technical Report Series, No. 996) (2016) ■ WHO *Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines* (Annex 8, WHO Technical Report Series, No. 996) (2016)

Table 2. **Contd**

Area	Overview of instruments
	■ WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (Annex 6, WHO Technical Report Series, No. 1003) (2017) ■ WHO *Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* (Annex 11, WHO Technical Report Series, No. 1010) (2018)
Selection, procurement and supply 	■ WHO *Guideline on good distribution practices for pharmaceutical products* (Annex 5, WHO Technical Report Series, No. 957) (2010) ■ WHO *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products* (Annex 9, WHO Technical Report Series, No. 961) (2011) ■ WHO *Model quality assurance system for procurement agencies* (Annex 3, WHO Technical Report Series, No. 986) (2014) ■ WHO *Guidelines on import procedures for pharmaceutical products* (Annex 5, WHO Technical Series, No. 1019) (2019) ■ WHO *Model list of essential medicines* (21st list, Annex 1, WHO Technical Series, No. 1019) (2019) ■ WHO *Model list of essential medicines for children* (7th list, Annex 2, WHO Technical Series, No. 1019) (2019) ■ WHO *Guideline on good storage and distribution practices for medical products* (Annex 7, WHO Technical Report Series, No. 1025) (2020)
Responsible and prudent use 	■ WHO *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses* ('the Blue Pocketbook') (2nd edition) (2010) ■ FIP/WHO *Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services* (2011) ■ WHO *Guidance for national tuberculosis programmes on the management of tuberculosis in children* (2014) ■ WHO *Revised WHO classification and treatment of childhood pneumonia at health facilities* (2014) ■ WHO *Guidelines for treatment of drug-susceptible tuberculosis and patient care* (2017) ■ WHO *AWaRe classification of antibiotics for evaluation and monitoring of use* (2019)
Disposal by the end user 	■ WHO *Safe management of wastes from health-care activities* (2nd edition, 2014)

Underlined text: instrument adopted by members.
Normal text: instrument not adopted by members. Details of the instruments can be found in Annex I.
Select publications outside of the scope of the compilation are mentioned for clarity in footnotes.

Summary

Standards related to the human use of antimicrobials are distributed over a large variety of instruments. No single comprehensive international instrument governs the use of antimicrobials in humans. Most instruments are technical guidelines adopted by the WHO Secretariat or expert committees supported by the WHO Secretariat.

3.1.1 Production

WHO has developed a variety of guidelines for ensuring quality in the production process which are compiled and published yearly in the reports of the WHO Expert Committee on Specification for Pharmaceutical Preparation (ECSPP), part of the Technical Report Series.[9]

The most relevant standards-setting documents for ensuring the quality of antimicrobials in the light of AMR are the ICH Q7 *Good manufacturing practice guide for active pharmaceutical ingredients* (2000), the identical WHO *Good manufacturing practices for active pharmaceutical ingredients* (Annex 2, WHO Technical Report Series, No. 957) (2010) and the WHO *Good manufacturing practices for pharmaceutical products: main principles* (Annex 2, WHO Technical Report Series, No. 986) (2014). In combination with the ICH Q10 *Pharmaceutical quality system* (2008), the WHO *Guidance on good practices for pharmaceutical quality control laboratories* (Annex 1, WHO Technical Report Series, No. 957) (2010), and the WHO *Guidelines on quality risk management* (Annex 2, WHO Technical Report Series No. 981) (2013), provide a frequently updated framework for ensuring the manufacturing of quality-assured pharmaceuticals, including antimicrobials.

A limited set of standards for environmental protection for the manufacturing of pharmaceuticals is provided in the ICH Q7 *Good manufacturing practice guide for active pharmaceutical ingredients* (2000), WHO *Good manufacturing practices for active pharmaceutical ingredients* (Annex 2, WHO Technical Report Series, No. 957) (2010) and WHO *Good manufacturing practices for pharmaceutical products: main principles* (Annex 2, WHO Technical Report Series, No. 986) (2014). Waste and wastewater management is also briefly addressed.

More detailed requirements regarding waste and wastewater management which can be applied to the production of antimicrobials are contained in the WHO *Good manufacturing practices for pharmaceutical products containing hazardous substances* (Annex 3, WHO Technical Report Series, No. 957) (2010). According to these guidelines, a hazardous substance or product is one that may present a substantial risk of injury to health or to the environment. Because antimicrobials released into the environment present a substantial risk of injury to both health and the environment, they are within the scope of this guidance.

In 2020, WHO developed guidance on the environmental aspects of good manufacturing practices (GMPs) for manufacturers and inspectors in preventing AMR: WHO *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance* (Annex 6, WHO Technical Report Series, No. 1025) (2020). The document directly addresses contamination of the environment with antimicrobials during production.

3.1.2 Regulatory evaluation and marketing authorization

Instruments on regulatory evaluation and marketing authorization are also collected in the annual ECSPP report that is published in the WHO Technical Report Series. The main international instruments on regulatory evaluation and marketing authorization can be found in the WHO *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory*

9 See Medicines quality assurance. In: WHO/Medicines and health products/Norms and standards: quality, safety and efficacy of medicines [website]. Geneva: World Health Organization; 2020 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/en/, accessed 17 August 2020).

authorities (NMRAs) (2nd edition) (2011). These references provide standards for good regulatory practice (GRP) and for the review of applications for marketing authorization of multisource (generic) pharmaceutical products. The text also provides references and standards for production and clinical trials. Many standards have been updated since its publication, and new standards added, including the WHO *General guidance on variations to multisource pharmaceutical products* (Annex 10, WHO Technical Report Series, No. 996) (2016) and the WHO *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (Annex 6, WHO Technical Report Series, No. 1003) (2017).

The packaging and labelling of pharmaceuticals is covered by the WHO *Guidelines on packaging for pharmaceutical products* (Annex 9, WHO Technical Report Series, No. 902) (2002). These guidelines provide standards for many aspects of packaging important for antimicrobial use, but do not cover specific standards to mitigate AMR, for instance specific standards for labelling, standards regarding promotional information or environmental aspects for disposal. Guidance for the safe disposal of medicines is captured in general, but no specific standards for antimicrobials.

The WHO Prequalification of Medicines Programme WHO provides a quality assurance mechanism that ensures that active pharmaceutical ingredients (APIs) and pharmaceutical products supplied by procurement agencies meet acceptable standards of quality, safety and efficacy following the above guidelines. The mechanism is described in the WHO *Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines* (Annex 8, WHO Technical Report Series, No. 996) (2016) and the WHO *Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* (Annex 11, WHO Technical Report Series, No. 1010) (2018). The list contains APIs and pharmaceutical products used to treat HIV/AIDS, tuberculosis (TB), malaria and other diseases, and for reproductive health.[10]

The WHO *Certification Scheme on the quality of pharmaceutical products moving in international commerce* provides countries with a voluntary agreement to provide assurance to countries participating in the Scheme on the quality of pharmaceutical products moving in international commerce including information on marketing authorization, manufacturing and adherence to GMPs.[11] The Scheme forms an important element in the quality assurance for international trade in pharmaceutical products.

There are no standards for the promotion of antimicrobials and medicines for human use in general, except for WHO's *Ethical criteria for medicinal drug promotion* adopted by the WHA in 1988.[12]

3.1.3 Selection, procurement and supply

Instruments on selection, procurement and supply are also collected in the annual ECSPP report. For the selection of medicines for human use, the most important international instrument is the WHO *Model List of Essential Medicines* (EML) (21st list, Annex 1, WHO Technical Series, No. 1019)) (2019), as well as the related

10 See WHO/Essential medicines and health products/Prequalification of medicines (website). Geneva: World Health Organization; 2020 (https://extranet.who.int/prequal/, accessed 17 August 2020).
11 See WHO/Essential medicines and health products/ Certification scheme on the quality of pharmaceutical products moving in international commerce (website). Geneva: World Health Organization; 2020 (https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/, accessed 17 August 2020).
12 Ethical criteria for medicinal drug promotion, Geneva: World Health Organization; 1988 (https://apps.who.int/iris/handle/10665/38125, accessed 20 June 2020).

WHO *Model list of essential medicines for children* (7th list, Annex 2, WHO Technical Series, No. 1019) (2019). The EML is reviewed every two years and provides a core list of essential medicine for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The EML also includes a complementary list of essential medicines for priority diseases, for which specialized diagnostic and monitoring facilities, and/or specialist medical care and/or specialist training are needed. The EML is used by many countries as the basis for developing/updating national formularies to guide procurement, among other purposes, as well as a model to develop more targeted national EMLs. The WHO EML provides specific categories for antibiotics, TB, multidrug-resistant (MDR)-TB and antifungals.

Based on the EML, WHO has developed the *AWaRe classification of antibiotics for evaluation and monitoring of use* (WHO AWaRe classification). It classifies antibacterials into "Access", "Watch" and "Reserve" groups to support access while ensuring good stewardship of antibiotics. The Access group contains antibacterials that are first- or second-line treatments for priority infectious syndromes; medicines in this group should be widely available, affordable and quality assured. The Watch group contains antibacterials that are considered to be at higher risk of resistance but are still recommended second-line treatments for narrow indications. The Reserve group comprises antibacterials that should be kept as a last resort.

For procurement and supply, the main standard is the WHO *Guideline on good distribution practices for pharmaceutical products* (2010), which provides general standards for ensuring the quality of medicines, but is not specific to antimicrobials. Other standards exist that, although they do not specifically mention antimicrobials, are applicable for antimicrobial use and to prevent or mitigate AMR (see Table 2 and Annex I).

3.1.4 Responsible and prudent use

The main instruments for governing appropriate human use of medicines in general are:

1. marketing approval procedures that define for which indication the antibiotic should be used and how to label medicines that come to the market; and
2. treatment guidelines that provide evidence-based recommendations on the treatment of certain syndromes.

As for medicines in general, comprehensive standards that govern marketing approval to ensure the safety, efficacy and quality of antibiotics exist at regional and national levels. For antimicrobials, the WHO AWaRe classification informs responsible and prudent use at the national, health-care facility and individual prescriber level.

At the global level, certain guidelines exist for treating specific infections – for instance HIV and malaria – and for treatment of children, the WHO *Pocket book of hospital care for children: guidelines for the management of common childhood illnesses* (2nd edition, 2010) that is covering infectious diseases such as sepsis, neonatal infections, pneumonia, diarrhoea, ear infections. However, there are no global treatment guidelines for the vast majority of bacterial infections (the exception being TB and the *WHO Guidance for national tuberculosis programmes on the management of tuberculosis in children* (2014)). The existing guidelines are also not always up to date and do not sufficiently take AMR into account.

For antimicrobial stewardship and antimicrobial stewardship programmes, there is no international instrument in the human health sector. There is, however, a basic standard for pharmacists – the *Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services* (2011) – that encourages pharmacies to be proactive in reducing AMR by providing guidance on the responsible and prudent use of antimicrobials to consumers and prescribers. There are also no international regulations that govern the sale of antimicrobials specifically, for instance, giving guidance on who should be allowed to prescribe and sell antimicrobials, or on restricting over-the-counter sales without a prescription.

For monitoring the use and consumption of antimicrobials, there is the *WHO methodology for a global programme on surveillance of antimicrobial consumption* (Version 1.0, 2018)[13] and the *WHO methodology for point prevalence survey on antibiotic use in hospitals* (Version 1.1, 2018).[14] But no instrument provides for or ensures their implementation.

The WHO AWaRe classification can guide stewardship interventions and analysis of antimicrobial use and consumption. The WHO 13th General Programme of Work includes an indicator based on AWaRe, which specifies that at the country level at least 60% of antibiotic consumption should be from medicines in the Access group. This indicator was included to monitor access to essential medicines and progress towards universal health coverage.[15]

3.1.5 Disposal by the end user

At the end of the antimicrobial life cycle, disposal is often guided by labels that provide information on how to safely dispose of unused and/or expired medicines. The *Safe management of wastes from health-care activities* (2nd edition, 2014) provides some best practices and standards for safe disposal in the healthcare sector. For the disposal of antimicrobials specifically, no guidance exists.

13 WHO methodology for a global programme on surveillance of antimicrobial consumption (Version 1.0), Geneva: World Health Organization; 2018 (https://www.who.int/medicines/areas/rational_use/WHO_AMCsurveillance_1.0.pdf, accessed 20 June 2020).

14 WHO methodology for point prevalence survey on antibiotic use in hospitals (Version 1.1). Geneva: World Health Organization; 2018 (https://apps.who.int/iris/bitstream/handle/10665/280063/WHO-EMP-IAU-2018.01-eng.pdf?ua=1, accessed 20 June 2020).

15 See WHO releases the 2019 AWaRe classification antibiotics. In: WHO/Medicines and health products/News/News 2019 (website). Geneva: World Health Organization; 2020 (https://www.who.int/medicines/news/2019/WHO_releases2019AWaRe_classification_antibiotics/en/, accessed 17 August 2020).

Box 1

Summary of core standards for human use

- Countries should aim to provide sustainable access to the antibiotics, TB and MDR-TB medicines and antifungals in the WHO EML.[16]
- At country level, by 2023 at least 60% of antibiotic consumption should be from medicines in the Access group of the AWaRe classification.[17]
- Pharmacists should be proactive in reducing AMR by providing guidance on the appropriate and prudent use of antimicrobials to consumers and prescribers.[18]
- Labels of pharmaceutical products should include any special storage conditions or handling precautions that may be necessary along with their directions for use, as well as any warnings and precautions that might be necessary.[19]
- Fixed-dose combinations should be rational, meaning that they take into account medical, quality and bioavailability considerations. An additional factor to consider is whether the combination reduces resistance creation.[20]

3.2 Overview and analysis of instruments on animal use

Table 3. Overview of instruments related to the animal use of antimicrobials across the antimicrobial life cycle

Area	Instruments
Production	■ FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005) (2005), §16–17, 39–43 ■ OIE *Terrestrial Animal Health Code* (2019), Chapter 6.10 ■ OIE *Aquatic Animal Health Code* (2019), Chapter 6.2
Regulatory evaluation and marketing authorization	■ VICH GL6 *Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – phase 1* (2000) ■ VICH GL38 *Environmental impact assessments (EIAs) for veterinary medicinal products (VMPs) – phase 2* (2004) ■ VICH GL27 *Pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance* (2004) ■ FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005) (2005), §9–38 ■ VICH GL36(R2) *Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI** (2019) ■ OIE *Terrestrial Animal Health Code* (2019), Chapters 3.1, 3.2 and 6.10 ■ OIE *Aquatic Animal Health Code* (2019), Chapters 3.1 and 6.2

16 WHO model list of essential medicines, 21st list. Geneva: World Health Organization; 2019 (https://www.who.int/medicines/publications/essentialmedicines/en/, accessed 17 August 2020).
17 The 2019 WHO AWaRe classification of antibiotics for evaluation and monitoring of use. Geneva: World Health Organization; 2019.
18 Good pharmacy practice. Joint FIP/WHO guidelines on GPP: standards for quality of pharmacy services. Geneva: World Health Organization; 2011.
19 WHO guidelines on packaging for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 9 (Technical Report Series, No. 902), p. 123.
20 WHO Guidelines for registration of fixed-dose combination medicinal products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 5 (Technical Report Series, No. 929), pp. 110–111.

Table 3. Cont.

Selection, procurement and supply 	■ FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005) (2005), §44–46 ■ FAO/WHO Codex Alimentarius *Guidelines for risk analysis of foodborne antimicrobial resistance* (CXG 77-2011) (2011) ■ OIE *Terrestrial Animal Health Code* (2019), Chapter 6.10 ■ OIE *Aquatic Animal Health Code* (2019), Chapter 6.2
Responsible and prudent use 	■ FAO/WHO Codex Alimentarius *Code of practice on good animal feeding* (CAC/RCP 54-2004) (2004) ■ FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005) (2005), §47–59 ■ FAO/WHO Codex Alimentarius *guidelines for the design and implementation of national regulatory food safety assurance programmes associated with the use of veterinary drugs in food producing animals* (CAC/GL 71-2009) (2009) ■ WHO *Guidelines on use of medically important antimicrobials in food-producing animals* (2017) ■ FAO/WHO Codex Alimentarius *Maximum residue limits (MRLs) and risk management recommendations (RMRs) for residues of veterinary drugs in foods* (CX/MRL2-2018) (2018) ■ WHO *Critically important antibiotics for human medicine ("WHO CIA list")* (6th edition) (2019) ■ OIE *List of antimicrobial agents of veterinary importance* (2019) ■ FAO *Prudent and efficient use of antimicrobials in pigs and poultry* (2019) ■ FAO *Aquaculture development. 8. Recommendations for prudent and responsible use of veterinary medicines in aquaculture* (2019) ■ OIE *Terrestrial Animal Health Code* (2019), Chapters 6.8, 6.9, 6.10 and 6.11 ■ OIE *Aquatic Animal Health Code* (2019), Chapters 6.2, 6.3, 6.4 and 6.5
Disposal by the end user 	■ FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005) (2005), §59 ■ OIE *Terrestrial Animal Health Code* (2019), Chapter 6.10 ■ OIE *Aquatic Animal Health Code* (2019), Chapter 6.2

Underlined text: instrument adopted by members.
Normal text: instrument not adopted by members. Details of the instruments can be found in Annex II.
Select publications outside of the scope of the compilation are mentioned for clarity in footnotes.
*ADI: acceptable daily intake.

Summary

Existing international instruments that provide standards for the animal use of antimicrobials are largely comprehensive and up to date, or in the process of being updated. Specific standards addressing antimicrobial use are fully integrated into the main instruments: the OIE *Terrestrial* and *Aquatic Animal Health Codes* and the Codex Alimentarius instruments. Currently, OIE *Codes* and the Codex Alimentarius Code of Practice are virtually harmonized. Nonetheless, standards may differ between them due to the mandate of the Codex Alimentarius which is to ensure food safety and OIE's mandate on improving animal health and welfare. Moreover, although both instruments are non-binding, they are international reference standards for the binding World Trade Organization (WTO) Sanitary and Phytosanitary Measures (SPS) and Technical Barriers to Trade (TBT) Agreements by reference (see Box 2). Both the OIE *Codes* and the Codex Alimentarius instruments were adopted by the members of the OIE and the Codex Alimentarius Commission, respectively, and provide opportunities for regular updating. The Codex Alimentarius *Code of Practice to Minimize and Contain Antimicrobial Resistance* is currently under revision. The upcoming version will include use of antimicrobials in plants and a section on food production.[21]

21 The FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* is currently under revision; the updated version will be released in 2021. The current draft (as of July 2020) can be found here (http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-804-07%252FREPORT%252FReport%252FREP20_AMRe.pdf, accessed 17 August 2020).

Box 2

The OIE *Codes* and Codex Alimentarius instruments as reference standards

The WTO SPS and TBT Agreements strike a balance between members' rights to regulate for legitimate objectives, such as food safety, consumer protection and animal health, and ensuring that such regulations do not become unnecessary or discriminatory barriers to trade.[22]

Both the WTO SPS and TBT Agreements encourage all members to participate in relevant standard-setting bodies and to use international standards, guidelines and recommendations as the basis for any trade-restricting measures. The OIE *Codes* and Codex Alimentarius instruments and guidelines are the main reference standards under the binding WTO SPS and TBT Agreements for antimicrobial use.

WTO SPS Agreement

The WTO SPS Agreement lays down the rules for trade related food safety, animal and plant health protection measures, to ensure that such measures do not constitute unnecessary barriers to trade. The agreement states that "to harmonize sanitary and phytosanitary measures on as wide a basis as possible, WTO members shall base their sanitary or phytosanitary measures on international standards, guidelines or recommendations, in this case the OIE Codes and the Codex Alimentarius code and guidelines".[23]

WTO TBT Agreement

The WTO TBT Agreement covers a wider variety of product standards. For AMU these mainly involve quality and labelling requirements. The WTO TBT Agreement states that "where technical regulations are required and relevant, international standards exist or their completion is imminent, WTO members shall use them or the relevant parts of them".[24]

3.2.1 Production

Instruments giving standards for animal use do not provide comprehensive standards for the production of antimicrobials for animal use or for veterinary pharmaceutical products in general. Often GMP for human use are applicable and applied to production for animal use as well. The OIE *Terrestrial* and *Aquatic Animal Health Codes* (2019; 2019), however, do refer to national GMPs. The FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005) provides additional standards for GMP that ensure quality. Similar standards are also applied to the manufacture of medicated feed containing antimicrobials.

3.2.2 Regulatory evaluation and marketing authorization

Regulatory evaluation and marketing authorization of antimicrobials for animal use are covered by the *OIE Terrestrial* and *Aquatic Animal Health Codes* (2019; 2019) and the FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005). Both instruments specifically emphasize identification of the competent authority and recognition of its functions, powers and mandate. The main focus of such an authority is to regulate the authorization of veterinary medical products, including labelling, packaging and surveillance; to monitor compliance; to grant marketing/manufacture authorization to veterinary pharmaceutical product producers, importers or distributors; and to set standards at the national level.

22 See World Trade Organization (website). Geneva: World Trade Organization; 2020 (https://www.wto.org/index.htm, accessed 17 August 2020).
23 Agreement on the Application of Sanitary and Phytosanitary Measures, Art. 3.1. Geneva: World Trade Organization; 1995.
24 Agreement on Technical Barriers to Trade, Art. 2.4. Geneva: World Trade Organization; 1995.

The OIE *Terrestrial Animal Health Code* (2019) is the main instrument for setting general standards for the market authorization process itself. The code states that veterinary legislation should ensure that only authorized veterinary pharmaceutical products are placed on the market, with special provisions for medicated feed and products prepared by authorized veterinarians or pharmacists.

In the specific chapters related to AMR of the OIE *Terrestrial Animal Health Code* (2019) and the OIE *Aquatic Animal Health Code* on responsible and prudent use of antimicrobial agents and the FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005), special standards apply to the authorization of antimicrobials with regard to market authorization; quality control; registration; labelling and packaging inserts; and post-marketing surveillance and supply. Also, an assessment is required of the risks to both animals and humans resulting from the use of antimicrobials in food-producing animals. This should be performed taking into account the individual and class of antimicrobials and the potential impact of use in food-producing animals on human and animal health. In addition, where possible, an assessment should also be done regarding the potential of the veterinary pharmaceutical product or its ingredients to select for resistance. The Veterinary International Conference on Harmonization (VICH) guideline GL27 *Pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance* (2004) gives broader guidance on the information required for pre-approval and specifically looks at AMR mechanisms and cross- and co-resistance. The OIE *Terrestrial Animal Health Code* (2019) also provides standards for countries lacking the necessary resources to implement an efficient registration procedure for veterinary medicines, including antimicrobials.

The OIE *Terrestrial Animal Health Code* (2019) states that all advertising of antimicrobials should be compatible with the principles of responsible and prudent use and should be controlled by advertising rules or standards. The relevant authorities must ensure that the advertising of these products complies with the marketing authorization granted, particularly regarding the content of the summary of product characteristics. Moreover, authorization is restricted to a veterinarian or other suitably trained person authorized to prescribe veterinary pharmaceutical products containing antimicrobial agents in accordance with the national legislation and under the supervision of a veterinarian.

For food safety, the OIE *Terrestrial Animal Health Code* (2019) requires listing maximum residue limits (MRLs) and withdrawal periods. The VICH GL36 (R2) *Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI* (2019) gives specifics for evaluating the safety of residues, including safety of antimicrobial residues on human intestinal flora.

The inclusion of labelling instructions for disposal and destruction and the obligation to follow good disposal practices is addressed in the OIE *Terrestrial and Aquatic Animal Health Codes* (2019; 2019). The FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005) gives the same labelling requirement and stipulates that relevant authorities should develop effective procedures for the safe collection and destruction of unused or expired veterinary antimicrobials. There are no standards for how collection and disposal should be performed and it is unclear whether these standards also apply to medicated feed containing antimicrobials. The VICH GL6 *Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – phase 1* (2000) and the VICH GL38 *Environmental impact assessments (EIAs) for veterinary medicinal products (VMPs) – phase 2* (2004) give specific guidelines for assessing the environmental impact of veterinary medicines.

3.2.3 Selection, procurement and supply

The OIE *Terrestrial and Aquatic Animal Health Codes* (2019; 2019) set standards for supply, calling for licensed or authorized distribution systems. The OIE *Terrestrial Animal Health Code* (2019) states that wholesale and retail distributors should have the responsibility of distributing and/or supplying veterinary antimicrobials only upon prescription of a veterinarian or other qualified professional authorized in accordance with national legislation and under the supervision of a veterinarian. The OIE *Codes* also require the distributor to ensure that the antimicrobials include instructions for proper disposal. The FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005) also has a chapter on the distribution of veterinary antimicrobial medicines with similar standards.

3.2.4 Responsible and prudent use

The OIE *Terrestrial* and *Aquatic Animal Health Codes* (2019; 2019) contain standards for the responsible and prudent use of antimicrobials as well as for the use of medicated feed. The OIE *Codes* call for prescription by a veterinarian or other trained person, as well as licensed or authorized distribution systems, and also call on food-producing animal producers to follow the veterinarian's prescription and the instructions on the pharmaceutical product itself. Disease-specific clinical guidelines on the use of antimicrobials in animals are not included in the OIE *Codes*.

The FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005) contains standards regarding education on use and a section on the responsibilities of veterinarians and producers. The code provides that producers of animals should not use antimicrobials as a replacement for good management and farm hygiene or other disease prevention methods such as vaccination, and should follow the product label. For feed specifically, the FAO/WHO Codex Alimentarius *Code of practice on good animal feeding* (CAC/RCP 54-2004) (2004) in section 4.5.1 on "feed additives and veterinary drugs used in medicated feed" states that antibiotics should not be used for growth-promoting purposes in the absence of a public health safety assessment.

The OIE *List of antimicrobial agents of veterinary importance* (2019) provides specific recommendations limiting the use of fluoroquinolones, third- and fourth-generation cephalosporins and colistin, including to urgently prohibit their use as growth promotors. These two classes, and colistin, should:

- not be used as a preventive treatment applied by feed or water in the absence of clinical signs in the animal(s) to be treated;
- not be used as a first-line treatment unless justified; when used as a second-line treatment, they should ideally be based on the results of bacteriological tests; and
- extra-label/off-label use should be limited and reserved for instances where no alternatives are available. Such use should be in agreement with the national legislation in force.

The WHO *Critically important antibiotics* (CIA) *for human medicine* (2019) classifies antimicrobials used in animals for their respective animal and human health importance and can guide the selection of antimicrobials. Furthermore, the WHO *Guidelines on use of medically important antimicrobials in food-producing animals* (2017) give recommendations for reducing the overall use of antimicrobials in animals, stopping the use of medically important antimicrobials for growth promotion and preventing their use in animals that have not been individually diagnosed.

The FAO manual *Prudent and efficient use of antimicrobials in pigs and poultry* (2019) provides guidance for appropriate and efficient use specifically in pigs and poultry. The manual suggests that antibiotics be phased out as growth promoters; that the use in animals of the highest priority on the CIA list be avoided; and that the recommendations of the OIE *List of antimicrobials of veterinary importance* be adhered to. The manual emphasizes the importance of using trained veterinarians and/or other animal health professionals, using antibiotics based on a diagnosis, ensuring the quality of veterinary medicines and properly disposing of unused or expired antibiotics. For aquaculture, the FAO's *Aquaculture development. 8. Recommendations for prudent and responsible use of veterinary medicines in aquaculture* (2019) emphasizes that the appropriate use of antimicrobial agents and other veterinary medicines in aquaculture production is a clinical decision that should be made based on experience and the local expertise of the prescribing aquatic animal health professional. For other species or groupings of animals no such instruments exist.

Monitoring antimicrobial use is comprehensively standardized in the OIE *Codes*.

For food safety, the FAO/WHO Codex Alimentarius *Maximum residue limits (MRLs) and risk management recommendations (RMRs) for residues of veterinary drugs in foods* specifies limits on antimicrobial residues. These Codex Alimentarius limits are informed through the frequent reports of the Joint FAO/WHO Expert Committee on Food Additives, which advises the Codex Committee on Residues of Veterinary Drugs in Foods.[25]

3.2.5 Disposal by the end user

At the end of the antimicrobial life cycle, disposal is often guided by the label of the veterinary medicines that should provide information on how to safely dispose of unused and/or expired veterinary medicines. The OIE *Terrestrial and Aquatic Animal Health Codes* (2019; 2019) focus on the end user and stipulate that disposal should be included in the training of all approved users. It is unclear whether this also applies to approved users of medicated feed containing antimicrobials. The FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (2005) states that producers of animals are responsible for proper disposal of such materials. There are no specific standards for the disposal of antimicrobials.

25 See WHO/Food safety/Areas of work/Chemical risks (website). Geneva: World Health Organization; 2020 (https://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/, accessed 17 August 2020).

Box 3

Summary of core standards for animal use

- For standards for animal use, national legislation should designate a veterinary authority and recognize its functions, powers and mandate.[26]
- Only authorized veterinary medicinal products should be placed on the market, with special provisions for medicated feed; products should be prepared by authorized veterinarians or pharmacists.[27]
- Relevant authorities should ensure that all the veterinary pharmaceutical products containing antimicrobial agents used in animals are prescribed by veterinarians or other authorized suitably trained persons and under the supervision of a veterinarian.[28]
- Veterinarians should only prescribe antimicrobial agents when necessary, based on good clinical examination and taking into consideration the OIE *List of antimicrobial agents of veterinary importance*, should provide exact dosage and should provide a detailed treatment protocol, including precautions and withdrawal times, especially when prescribing extra-label or off-label use.[29]
- Distribution of the veterinary pharmaceutical products and medicated feed containing antimicrobial agents should only be done when prescribed by veterinarians or other authorized suitably trained persons and under the supervision of a veterinarian.[30]
- All advertising of antimicrobial agents should follow the principles of responsible and prudent use and be restricted to veterinarians or other persons authorized to prescribe veterinary pharmaceutical products containing antimicrobials and should be controlled by codes of advertising standards.[31]
- For the marketing and export of veterinary medical products (VMPs) containing antimicrobial agents, only licensed and officially approved veterinary pharmaceutical products containing antimicrobial agents should be sold and supplied, and then only through licensed/authorized distribution systems.[32]
- Labels of veterinary pharmaceutical products containing antimicrobial agents should contain the APIs and class; pharmacological properties; potential adverse effects; target animal species and, as appropriate, age or production category; therapeutic indications; target microorganisms; dosage regimen and route of administration; withdrawal periods; incompatibilities and interactions; storage conditions and shelf-life; operator safety; particular precautions before use; particular precautions for the proper disposal of un-used or expired products; information on conditions of use relevant to the potential for selection of resistance; and contraindications.[33]
- Veterinarians and producers should follow the disposal guidance on the label.[34]

26 OIE Terrestrial Animal Health Code, Art. 3.4.11 and 6.10.3 (Paris: World Organisation for Animal Health; 2018) (hereinafter OIE Terrestrial Code); FAO/WHO Codex Alimentarius Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005), §9-16 (Geneva: World Health Organization; 2005) (hereinafter FAO/WHO CXC 61-2005).
27 OIE Ter, Chapter 3.4.11.
28 OIE Ter, Art. 6.10.3.; FAO/WHO CXC 61-2005, §13.
29 OIE Ter, Art. 6.10.6. and OIE List of antimicrobial agents of veterinary importance.
30 OIE Ter, Art. 6.10.6. and 6.10.8.; FAO/WHO CXC 61-2005, §34.
31 OIE Ter, Art. 6.10.3.; FAO/WHO CXC 61-2005, §35 and 41.
32 OIE Ter, Art. 6.10.4.
33 OIE Ter, Art. 6.10.3.
34 OIE Ter, Art. 6.10.3. and 6.10.7.

3.3 Overview and analysis of instruments on plant use

Table 4. Overview of instruments related to the plant use of antimicrobials across the antimicrobial life cycle

Area	Instruments
Production 	■ FAO/WHO *International code of conduct on pesticide management* (2014) ■ FAO/WHO *Guidelines on pesticide legislation* (2015)
Regulatory evaluation and marketing authorization 	■ FAO/WHO *Guidelines for the registration of pesticides* (2010) ■ FAO/WHO *Guidelines on pesticide advertising* (2010) ■ FAO/WHO *International code of conduct on pesticide management* (2014) ■ FAO/WHO *Guidelines on pesticide legislation* (2015) ■ FAO/WHO *Guidelines on good labelling practice for pesticides* (2015) ■ UN *Globally harmonized system of classification and labelling of chemicals* (GHS or "the Purple Book") (8th revised edition) (2019)
Selection, procurement and supply 	■ FAO/WHO *International code of conduct on pesticide management* (2014) ■ FAO/WHO *Guidelines on pesticide legislation* (2015)
Responsible and prudent use 	■ FAO *Guidelines on prevention and management of pesticide resistance* (2012) ■ FAO/WHO *International code of conduct on pesticide management* (2014) ■ FAO/WHO *Guidelines on pesticide legislation* (2015) ■ FAO/WHO Codex Alimentarius *Codex pesticides residues in food online database* (2019)
Disposal by the end user 	■ FAO/WHO *International code of conduct on pesticide management* (2014) ■ FAO/WHO *Guidelines on pesticide legislation* (2015) ■ FAO *Environmental management tool kit for obsolete pesticides – volume 1, volume 2, volume 3, volume 4, volume 5 and volume 6* (respectively 2009, 2009, 2011, 2011, 2020 and 2020)

Normal text: instrument not adopted by members. Details of the instruments can be found in Annex III.
Select publications outside of the scope of the compilation are mentioned for clarity in footnotes.

Summary

The main instrument for the use of antimicrobials in plants is the FAO/WHO International code of conduct on pesticide management, underpinned by various guidelines from FAO and WHO. General instruments for pesticide use are available, but specific guidance is lacking on the use of antimicrobial pesticides. The Codex Alimentarius Code of practice to minimize and contain AMR is currently under revision and will include antimicrobial use in plants.[19]

Box 4

AMR and plant use

The Commission on Phytosanitary Measures that governs the International Plant Protection Convention has acknowledged that "large volumes of antimicrobials are applied to crops to control plant pests", that "the overuse or misuse of antimicrobials can also trigger the development of resistant microorganisms relevant to human and animal health" and that "there is scientific evidence that foods of plant origin serve as a vehicle for foodborne exposure to resistant bacteria". Precautionary preventative measures "could play an important role in multi-sectoral efforts to decrease the risks with AMR".[35] A joint FAO/WHO expert group also acknowledges that there is "clear scientific evidence that foods of plant origin serve as vehicles of foodborne exposure to antimicrobial-resistant bacteria". [36]

3.3.1 Production

The FAO/WHO *International code of conduct on pesticide management* (ICoCPM) (2014) provides standards for regulating the production of pesticides and some quality standards for manufacturers. The FAO/WHO *Guidelines on pesticide legislation* (2015) reflect these standards in relation to implementation in national law and put special emphasis on licensing of manufacturers. Currently, no international environmental standards exist governing the manufacture of pesticides, other than the ICoCPM and its implementing guidelines.

3.3.2 Regulatory evaluation and marketing authorization

These standards are mainly covered by the FAO/WHO *International code of conduct on pesticide management* (2014) and the FAO/WHO *Guidelines on pesticide legislation* (2015). The FAO/WHO *Guidelines for the registration of pesticides* (2010) reflect the provisions of these documents and set standards for national authorities and procedures.

The code of conduct and the FAO/WHO *Guidelines on pesticide advertising* (2010) recommend that national governments and the pesticide industry should be truthful and not publicly advertise pesticides whose use is legally restricted.

The code of conduct and the FAO/WHO *Guidelines on good labelling practice for pesticides* (2015) recommends that the package includes information and instructions to "minimize risks to users, the public and the environment". The guidelines provide specific standards for label content, including hazard and safety information and directions for use, including disposal of leftover pesticides. The UN *Globally harmonized system of classification and labelling of chemicals* (2019) covers the specific labelling of chemicals, including some pesticides, but does not cover antimicrobials or AMR.

3.3.3 Selection, procurement and supply

The FAO/WHO *International code of conduct on pesticide management* (2014) covers the distribution and trade of pesticides, including the recommendation that pesticides should be traded by and purchased from reputable traders and that persons involved in the sale of pesticides should be trained adequately.

35 Antimicrobial Resistance (AMR) in relation to plant health aspects. In: Commission on Phytosanitary Measures, 14th Session, Rome, 1–5 April 2019. Agenda Item 8.9. Rome: International Plant Protection Convention; 2019 (CPM 2019/INF/12, https://www.ippc.int/static/media/files/publication/en/2019/02/INF_12_CPM_2019_AMR-2019-02-20.pdf, accessed 1 July 2020).

36 Joint FAO/WHO Expert Meeting in collaboration with OIE on foodborne antimicrobial resistance: role of the environment, crops and biocides. Rome: Food and Agriculture Organization of the United Nations; 2019 (http://www.fao.org/3/ca6724en/ca6724en.pdf, accessed 1 July 2020).

The FAO/WHO *Guidelines on pesticide legislation* (2015) gives guidance regarding these standards for national implementation.

3.3.4 Responsible and prudent use

The FAO/WHO *International code of conduct on pesticide management* (2014) covers the use of pesticides, including restricting use, which the code leaves mainly to national authorities. The FAO *Guidelines on prevention and management of pesticide resistance* cover resistance in fungicides, herbicides, insecticides and rodenticides, with the objective of maintaining effective pesticides for plant use. The FAO/WHO *Guidelines on pesticide legislation* (2015) provide guidance regarding these standards for national implementation. No specific instrument or standards exist for antimicrobials.

For food safety, the Codex Alimentarius Commission has adopted pesticide MRLs for certain antimicrobials, namely pesticides, fungicides and other anti-parasitics in the FAO/WHO Codex Alimentarius *Codex pesticides residues in food online database* (2019).

3.3.5 Disposal by the end user

The FAO/WHO *International code of conduct on pesticide management* (2014) covers disposal as a responsibility of mainly governments and industry, but does not specifically address antimicrobials or the responsibility of the individual. The FAO *Environmental management tool kit for obsolete pesticides volumes 1–6* (2009–2020) gives more detailed guidance for disposal of obsolete pesticides but does also not specifically address antimicrobials. The FAO/WHO *Guidelines on pesticide legislation* (2015) provides guidance regarding these standards for national implementation.

Summary of core standards for plant use

- National governments and the pesticide industry should be truthful and pesticides that have been legally restricted should not be publicly advertised.[37]
- The packaging of pesticides should include information and instructions to minimize risks to users, the public and the environment.[38]
- The pesticide industry should endeavour to ensure that pesticides are traded by and purchased from reputable traders, who should preferably be members of a recognized trade organization, and that persons involved in sales are trained adequately, hold appropriate government permits or licenses, and have access to information.[39]
- Governments, with the help of the pesticide industry, and with multilateral cooperation, should inventory obsolete or unusable stocks of pesticides and used containers, establish and implement an action plan for their disposal (or remediation, in the case of contaminated sites), and record these activities.[40]

37 FAO/WHO International code of conduct on pesticide management, Art. 11 [hereinafter FAO/WHO international code of conduct].
38 FAO/WHO International code of conduct, Art. 3 and FAO/WHO Guidelines on good labelling practice for pesticides.
39 FAO/WHO International code of conduct, Art. 8.
40 FAO/WHO International code of conduct, Art. 10; Environmental management toolkit for obsolete pesticides, vols. 1 and 2. FAO Pesticide Disposal Series, Nos. 12 and 13. Rome: Food and Agriculture Organization of the United Nations; 2009.

3.4 Overview and analysis of antimicrobial use and the environment

Table 5. Overview of instruments per area of use with standards related to the environment

Area	Instruments with standards related to the environment of antimicrobials
Human use 	▪ ICH Q7 *Good manufacturing practice guide for active pharmaceutical ingredients* (2000) / WHO *Good manufacturing practices for active pharmaceutical ingredients* (Annex 2, WHO Technical Report Series, No. 957) (2010) (adopts the ICH Q7 above and is identical) ▪ WHO *Good manufacturing practices for pharmaceutical products containing hazardous substances* (Annex 3, WHO Technical Report Series, No. 957) (2010) ▪ WHO *Good manufacturing practices for pharmaceutical products: main principles* (Annex 2, WHO Technical Report Series, No. 986) (2014) ▪ WHO *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance* (Annex 6, WHO Technical Report Series, No. 1025) (2020)
Animal use 	▪ VICH GL6 *Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – phase 1* (2000) ▪ VICH GL38 *Environmental impact assessments (EIAs) for veterinary medicinal products (VMPs) – phase 2* (2004) ▪ FAO/WHO Codex Alimentarius *Code of practice to minimize and contain antimicrobial resistance* (CXC 61-2005) (2005), §7 and 59 ▪ FAO *Aquaculture development. 8. Recommendations for prudent and responsible use of veterinary medicines in aquaculture* (2019) ▪ OIE *Terrestrial Animal Health Code* (2019), Chapters 6.10 and 6.11 ▪ OIE *Aquatic Animal Health Code* (2019), Chapters 6.2 and 6.5
Plant use 	▪ FAO/WHO *Guidelines for the registration of pesticides* (2010) ▪ FAO/WHO *Guidelines on pesticide advertising* (2010) ▪ FAO *Guidelines on prevention and management of pesticide resistance* (2012) ▪ FAO/WHO *International code of conduct on pesticide management* (2014) ▪ FAO/WHO *Guidelines on good labelling practice for pesticides* (2015) ▪ FAO/WHO *Guidelines on pesticide legislation* (2015) ▪ UN *Globally harmonized system of classification and labelling of chemicals* (GHS or "the Purple Book") (8th revised edition) (2019) ▪ FAO *Environmental management tool kit for obsolete pesticides – Volume 1, Volume 2, Volume 3, Volume 4, Volume 5* and *Volume 6* (respectively 2009, 2009, 2011, 2011, 2020 and 2020)

Underlined text: instrument adopted by members.
Normal text: instrument not adopted by members. Details of the instruments can be found in Annexes I, II and III.
Select publications outside of the scope of the compilation are mentioned for clarity in footnotes.

Summary

Different instruments cover antimicrobials and chemicals that impact the environment, establishing directives and policies for the production, trade, use and release of these antimicrobials and chemicals into the environment. The main focus of the instruments is the sound management of the products or substances throughout their life cycle, particularly in their final stage, i.e. waste management. Furthermore, given that water, sanitation, hygiene and wastewater factors play a key role in the environmental dispersal and transmission of AMR, instruments that provide environmental quality standards to protect water are also considered.

As shown in Table 5, environmental aspects are mostly included in sector-specific instruments and covered in their respective chapters. Antimicrobials could also potentially fall within the scope of numerous other international instruments relating to the environment, but they do not all have the same type of impact on the use of antimicrobials.

The connection between antimicrobial use and the environmental instruments included in this compilation are twofold: the purpose of the instrument and the effect of the standards. The purpose or intent of the instruments considered should include the antimicrobial substances due to their antimicrobial properties and not for other environmental reasons. The effect of the provisions should be guide how antimicrobials are used. In this respect, there is a scarcity of international instruments that provide these environmental standards.

3.4.1 Chemicals and waste management

Some international chemical conventions (the Stockholm Convention on Persistent Organic Pollutants;[41] the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade;[42] and the Basel Convention on the Control of Transboundary Movements of Hazardous Waste and Their Disposal[43]) were considered in examining the connection between the environment and antimicrobials but were not included in the compilation. Although the conventions include some substances that are also used as antimicrobials (for instance, various persistent organic pollutants used as antifungals[44]), their inclusion was not based on the antimicrobial properties of the substances in question or the risks they pose to the development and spread of AMR. These instruments do, however, provide an opportunity to address AMR, as they delineate existing mechanisms that govern the use, trade and disposal of hazardous chemicals, products and waste, including the setting, monitoring and enforcing of national guidelines.

41 See Stockholm Convention [website]. Geneva: Stockholm Convention; 2020 (http://www.pops.int, accessed 17 August 2020).
42 See Rotterdam Convention [website]. Geneva: Rotterdam Convention; 2020 (http://www.pic.int/, accessed 17 August 2020).
43 See Basel Convention [website]. Geneva: Basel Convention; 2020 (http://www.basel.int/, accessed 17 August 2020).
44 For example hexachlorobenzene; pentachlorobenzene; pentachlorophenol, its salts and esters (PCP).

Box 6

Antimicrobial use and the environment

Antimicrobials can impact ecosystems when they are released during production, consumption, disposal and/or inappropriate discharge. The release of antimicrobials or other chemical substances into the environment – from households, hospital effluents, animal and manufacturing plant run-off – can result in concentrations of these substances, mainly in surface waters such as lakes and rivers, but also in sewage effluent, groundwater, soil and manure, and even in drinking water. Anthropogenic activities are increasing the importance of the environment as a pathway for AMR human exposure.

Selective pressure from antibiotic residues, biocidal substances (or chemicals with antimicrobial properties, e.g. disinfectants, antiseptics, detergent, cosmetics, food preservatives), heavy metals (e.g. silver, zinc, copper, chromium, lead), PAHs (polycyclic aromatic hydrocarbons) and antidepressants on bacterial communities may contribute to increased AMR in the environment.[45]

3.4.2 UNECE protocols

One binding instrument that could cover the use of antimicrobials is the United Nations Economic Commission for Europe (UNECE) Convention on Environmental Impact Assessment in a Transboundary Context[46] (known as the Espoo Convention, 1991) and the complementary protocol addressing pollution control mechanisms, the United Nations Protocol on Strategic Environmental Assessment to the Convention on Environmental Impact Assessment in a Transboundary Context[47] (2003). The Espoo Convention and the protocol set out the obligations of parties to assess the transboundary environmental impact of certain activities at an early stage of planning. In particular, the protocol includes not only a focus on human health (see Article 5, paragraph 1; Annex 3) but also projects related to API and pharmaceutical production, as well as intensive livestock (including poultry) and fish farming, and specific types of waste management (Annex 2). The strategic environmental assessment specified by the protocol could form a starting point for reducing antimicrobials in the environment. However, the protocol has only been adopted by 33 countries, most of which are in Europe. Moreover, evidence for the environmental impact of antimicrobials remains limited and is therefore currently unlikely to be included in such assessments.

Another opportunity might lie in the binding United Nations Protocol on Pollutant Release and Transfer Registers to the Convention on Access to Information, Public-Participation in Decision-Making and Access to Justice in Environmental Matters (2003)[48] to the UNECE Convention on Access to Information, Public Participation in Decision-making and Access to Justice in Environmental Matters (known as the Aarhus Convention, 1998). This protocol requires countries to set up publicly available pollutant release and transfer registers from industrial sites and other sources, including intensive rearing of poultry and pigs and intensive aquaculture, waste and water management, and API and pharmaceutical production (Annex 1). Although regulating information on pollutants, rather than pollution directly, the protocol is expected to exert significant downward pressure on levels of pollution, as no company will want to be

45 Gaze W, Depledge M. Antimicrobial resistance: investigating the environmental dimension – frontiers 2017: emerging issues of environmental concern. Nairobi: United Nations Environment Programme; 2017 (http://wedocs.unep.org/handle/20.500.11822/22263, accessed 1 June 2020).

46 See Convention on environmental impact assessment in a transboundary context. Geneva: United Nations Economic Commission for Europe; 2005 (ECE/MP.EIA/21; https://www.unece.org/index.php?id=40450&L=0, accessed 17 August 2020).

47 See Protocol on strategic environmental assessment to the convention on environmental impact assessment in a transboundary context, Chapter 27, Environment, 4.b. United Nations Treaty Collection. New York: United Nations; 2020 (https://treaties.un.org/Pages/ViewDetails.aspx?src=TREATY&mtdsg_no=XXVII-4-b&chapter=27&lang=en, accessed 17 August 2020.

48 See Introduction: Kyiv protocol on pollutant release and transfer registers. In: UNECE/Environmental Policy/Protocols on PRTRs/Introduction [website]. Geneva: United Nations; 2020 (https://www.unece.org/env/pp/prtr.html, accessed 17 August 2020).

identified as being among the biggest polluters. Currently, the list of pollutants (Annex 2) does not include antimicrobials. Moreover, the protocol has been adopted by 37 countries, most of which are in Europe. Nonetheless, the system of pollutant release and transfer registers could well include antimicrobials through an additional instrument.

3.4.3 Water management

No standards for water management relate specifically to antimicrobial use and AMR, though the important role of water, hygiene and sanitation more broadly in AMR, including water management, is evident.[49] WHO provides some guidance on pharmaceuticals in wastewater, showing that in many countries certain antibiotics are found in the drinking water supply.[50] UNEP has produced various protocols providing standards regarding the environmentally sound management of pesticides and/or persistent organic pollutants that could include certain antimicrobials.[51]

3.4.4 Soil health

A non-binding environment-related instrument of importance for antimicrobial use is the FAO *Voluntary guidelines for sustainable soil management*,[52] which lays out a general standard of care for the prevention of soil pollution and the maintenance of microbial life in soil.

In short, some international instruments do address certain dimensions of the environmental impact of antimicrobials that could affect their use, but those instruments are limited to the human, animal and plant sections of this compilation. No international instruments exist that specifically address the impact of antimicrobials on the environment and that could influence their use.

49 FAO/OIE/WHO. Technical brief on water, sanitation, hygiene and wastewater management to prevent infections and reduce the spread of antimicrobial resistance. Geneva: World Health Organization; 2020 (http://www.fao.org/3/ca9120en/ca9120en.pdf, accessed 17 August 2020).

50 Pharmaceuticals in drinking-water. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/44630, accessed 17 August 2020).

51 UNEP/CHW.13/6/Add.1/Rev.1. General technical guidelines on the environmentally sound management of wastes consisting of, containing or contaminated with persistent organic pollutants. Nairobi: United Nations Environment Programme; 2017; UNEP/CHW.12/5/Add.9. Technical guidelines on the environmentally sound management of wastes consisting of, containing or contaminated with the pesticides. Nairobi: United Nations Environment Programme; 2015.

52 Voluntary guidelines on soil management. Rome: Food and Agriculture Organization of the United Nations; 2017 (http://www.fao.org/3/a-bl813e.pdf, accessed 17 August 2020).

Monitoring implementation of international standards on the use of antimicrobials

4.1 Implementation at the national level

The Global Action Plan on AMR emphasized the need for national governments to take action to contain AMR, including the development of national action plans (NAPs) following the One Health approach. Many NAPs contain planned changes in national instruments and standards, including harmonization with international standards. This compilation will assist national authorities in their efforts to adapt and adopt relevant international instruments and standards. Most countries have historically enacted laws, regulations, policies or other instruments addressing some aspect of standards for medicines, veterinary medicines, pesticides and chemical controls. However, such measures constitute only one part of a broad spectrum of regulatory areas with implications for antimicrobial use and AMR. Standards on antimicrobial use should be implemented in a comprehensive manner covering the five stages of the antimicrobial life cycle: production, regulatory evaluation and marketing authorization, selection, procurement and supply, and responsible, prudent use and disposal. This requires effective national legal and policy frameworks, leadership commitment, functions systems and the availability of financial resources. Furthermore, efficient enforcement mechanisms by the relevant authorities and the necessary technical capacity are critical for the implementation of these standards and instruments.

4.2 Tripartite monitoring of standards implementation

To monitor country progress in implementing their NAPs, an annual Tripartite AMR Country Self-assessment Survey (TrACSS) has been jointly undertaken by FAO, the OIE and WHO since 2016.[53] The 2019–2020 (TrACSS 4.0)[54] survey contained several questions regarding standards on the use of antimicrobials (see Annex IV).

The Tripartite has also developed the *Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators*[55] that includes indicators on antimicrobial use relevant to this compilation.

53 See Global monitoring of country progress on addressing antimicrobial resistance: self-assessment questionnaire 2019–2020. Geneva: World Health Organization; 2020. (https://www.who.int/antimicrobial-resistance/global-action-plan/monitoring-evaluation/AMR-country-self-assessment-2019/en/, accessed 17 August 2020).

54 See Tripartite AMR country self-assessment survey (TrACSS). Geneva: World Health Organization; 2020 (https://www.who.int/antimicrobial-resistance/global-action-plan/monitoring-evaluation/AMR-country-questionnaire-4.0-November-2019.pdf, accessed 17 August 2020).

55 See Monitoring and evaluation of the global action plan on antimicrobial resistance: framework and recommended indicators. Geneva: World Health Organization, 2019 (https://apps.who.int/iris/handle/10665/325006, accessed 17 August 2020).

4.3 Monitoring implementation of standards for human use

In addition to the TrACSS, WHO supports joint external evaluation (JEE) on country implementation of the International Health Regulations (2005)[56], which includes an action package on AMR since 2018.[57] In particular, P3.4 focuses on optimizing use of antimicrobial medicines in human and animal health and agriculture, including whether there are national regulations or policies.[58]

4.4 Monitoring implementation of standards for animal use

The Performance of Veterinary Services (PVS) Pathway focuses on the quality of veterinary services and the implementation of chapters of the *Terrestrial Animal Health Code* and chapters of the *Aquatic Animal Health Code*. Based on a specific tool,[59] the OIE trained PVS experts to carry out evaluation of national veterinary services and to provide countries with a comprehensive understanding of their veterinary service strengths and weaknesses. Following PVS Evaluation missions, countries are offered the choice by the OIE to keep their mission reports confidential or to approve the their publication. The PVS Evaluations only provide a partial picture of the antimicrobial use situation, but have been strengthened with the addition of a critical competency on AMR to better reflect AMR issues. In addition, the OIE Veterinary Legislation Support Programme (VLSP), a component of the PVS Pathway, has developed a specific module which aims at assessing, in depth, a country's AMR-relevant legislation in the veterinary domain.

The OIE has been collecting animal AMU data collection, worldwide, for the past five years. The methodology used in this data collection was developed, according to the related standards of the *OIE Terrestrial* and *Aquatic Animal Health Codes*. This data collection is therefore a way of monitoring the implementation of standards in animal use.

Furthermore, in May 2018, the World Assembly of OIE Delegates adopted Resolution No. 36[60] recommending the establishment of an observatory on the implementation of OIE standards by member countries. The implementation of the OIE Observatory will start at the end of 2020. As the OIE Observatory will initially focus on key standards, it may include some standards related to antimicrobial use.

56 See International health regulations, 3rd edition. Geneva: World Health Organization; 2005 (https://www.who.int/ihr/publications/9789241580496/en/, accessed 17 August 2020).

57 See Joint external evaluation tool (JEE tool), 2nd edition. International Health Regulations (2005) monitoring and evaluation framework. Geneva: World Health Organization; 2005 (https://www.who.int/ihr/publications/WHO_HSE_GCR_2018_2/en/, accessed 17 August 2020).

58 See WHO/International Health Regulations/IHR procedures and implementation/Strengthening health security by implementing the International Health Regulations (website). Geneva: World Health Organization; 2020 (https://www.who.int/ihr/procedures/mission-reports/en/, accessed 17 August 2020).

59 See PVS tool 2019: OIE tool for the evaluation of performance of veterinary services, 7th edition. Paris: World Organisation for Animal Health; 2019 (https://www.oie.int/fileadmin/Home/eng/Support_to_OIE_Members/docs/pdf/2019_PVS_Tool_FINAL.pdf), accessed 17 August 2020) and OIE PVS tool: aquatic: OIE tool for the evaluation of performance of veterinary services and/or aquatic animal health services. Paris: World Organisation for Animal Health; 2013 (https://www.oie.int/fileadmin/Home/eng/Support_to_OIE_Members/pdf/A_PVS_Tool_aquatic_animals.pdf, accessed 17 August 2020).

60 Veterinary Legislation Support Programme (VLSP) mission reports can be found on the OIE website, see https://www.oie.int/fileadmin/Home/eng/Internationa_Standard_Setting/docs/pdf/Observatory/A-Reso_36.pdf.

FAO has developed a methodology for analysing AMR-relevant legislation in the food and agriculture sector. In addition to the abovementioned OIE VLSP specific module, the OIE has provided inputs to this FAO methodology. The FAO methodology promotes a review process that helps reveal gaps in national AMR and antimicrobial use legislation and can help assess the compatibility of various types of national and regional legal instruments with international standards for addressing AMR.

4.5 Monitoring implementation of standards for plant use

In addition the question related to legislation on the marketing of and monitoring the use of pesticides, including antimicrobial pesticides in TrACSS, in 2018, WHO and FAO conducted a global survey to describe the current situation regarding pest management in agriculture and public health.[61] The survey questionnaire was based on the FAO/WHO *International code of conduct on pesticide management* (2014). While the survey did not address antimicrobial use or AMR, it does assess which countries have guidelines and capacity for pesticide registration. Furthermore, the survey covers safe storage, transport and disposal of pesticides, as well as whether countries have a system for monitoring pesticide residues in food/feed items and in the environment. The survey addressed monitoring and enforcement, and whether countries require licensing or certification of agricultural pesticide applicators.

Additionally, the FAO *Methodology to analyze AMR-relevant legislation in the food and agriculture sector* includes the analysis of legislation on antimicrobials for plant use, focusing on the national regulatory framework governing pesticides.

4.6 Monitoring implementation of standards for the environment

TrACSS has one wide-ranging question addressing legislation or regulation to prevent contamination of the environment with antimicrobials, including discharge and disposal. Furthermore, the FAO *Methodology to analyze AMR-relevant legislation in the food and agriculture sector* includes an analysis of legislation on environmental protection, paying attention to the critical regulatory points where antimicrobials may impact on the environment.

61 See Global situation of pesticide management in agriculture and public health: report of a 2018 WHO–FAO survey. Geneva: World Health Organization; 2019 (http://www.fao.org/3/ca7032en/ca7032en.pdf, accessed 17 August 2020).

Annex I: List of international instruments on the use of antimicrobials across the human sector

	Name	Last updated	Type	Organization
1. Production 	Q7 Good manufacturing practice guide for active pharmaceutical ingredients	2000	Guideline	ICH
	Q10 Pharmaceutical quality system	2008	Guideline	ICH
	Good manufacturing practices for pharmaceutical products containing hazardous substances (Annex 3, WHO Technical Report Series, No. 957)	2010	Guideline	WHO
	Good manufacturing practices for active pharmaceutical ingredients (Annex 2, WHO Technical Report Series, No. 957)	2010	Guideline	WHO
	Good practices for pharmaceutical quality control laboratories (Annex 1, WHO Technical Report Series, No. 957)	2010	Guideline	WHO
	Guidelines on quality risk management (Annex 2, WHO Technical Report Series, No. 981)	2013	Guideline	WHO
	Good manufacturing practices for pharmaceutical products: main principles	2014	Guideline	WHO

Coverage	Legal status	Approval process	Implementable standards
GMP guidance for the manufacturing of APIs under an appropriate system for managing quality	Non-binding	The ICH builds on a formal process of technical harmonization among regulatory agencies that culminates with the implementation of the guideline in countries (Stage 5).	GMP standards for the manufacturing of APIs in general, with a particular focus on quality management, packaging and identification labels of APIs and intermediates, storage and distribution, and complaint mechanisms. It does not provide specific standards for antimicrobials or AMR; however, the chapter on GMPs for API production through fermentation is also applicable to the manufacturing antimicrobials.
A model for an effective quality management system for the pharmaceutical industry	Non-binding	The ICH builds on a formal process of technical harmonization among regulatory agencies that culminates with the implementation of the guideline in countries (Stage 5).	Provides a model that includes standards for quality management, improvement of process performance and product quality, but does not provide specific standards for antimicrobials or AMR.
GMP guidelines for pharmaceutical products and APIs that contain hazardous substances, mainly focusing on certain hormones, steroids and cytotoxins	Non-binding	WHO Guidelines Review Committee	Standards for pharmaceutical products and APIs that contain hazardous substances. Because of the impact antimicrobials have on the environment, they can be considered hazardous. Primarily sets standards for personal protection and environmental protection and can apply to antimicrobials.
GMP guidance for the manufacturing APIs under an appropriate system for managing quality	Non-binding	WHO Guidelines Review Committee	Standards that are directly based on the IHC Q7 Good manufacturing practice guide for active pharmaceutical ingredients (2000)
Advice on the quality management system within which the analysis of APIs, excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.	Non-binding	WHO Guidelines Review Committee	Standards for management and infrastructure, materials, equipment, instruments, etc., as well as for working procedures and safety; does not specifically address antimicrobials or AMR.
Guidance to assist the development and implementation of effective quality risk management (QRM), covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution.	Non-binding	WHO Guidelines Review Committee	Standards for the QRM process, including the process, application for pharmaceuticals for manufacturers and for medicines regulatory authorities.
GMP guidance for pharmaceutical products	Non-binding	WHO Guidelines Review Committee	Standards for GMPs for pharmaceutical products in general, with a particular focus on quality management, personnel, qualification and validation, complaints, product recalls, materials and documentation. Provides no specific standards for antimicrobials.

	Name	Last updated	Type	Organization
1. Production Cont.	Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance (Annex 6, WHO Technical Report Series, No. 1025)	2020	Guideline	WHO
2. Market authorization and regulatory approval 	Guidelines on packaging for pharmaceutical products	2002	Guideline	WHO
	Guidelines for registration of fixed-dose combination medicinal products	2005	Guideline	WHO
	Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for National Medicines Regulatory Authorities (NMRAs) (2nd edition)	2011	Manual	WHO
	General guidance on variations to multisource pharmaceutical products (Annex 10, WHO Technical Report Series, No. 996)	2016	Guideline	WHO
	Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines (Annex 8, WHO Technical Report Series, No. 996)	2016	Guideline	WHO
	Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability (Annex 6, WHO Technical Report Series, No. 1003)	2017	Guideline	WHO
	Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (Annex 11, WHO Technical Report Series, No. 1010)	2018	Guideline	WHO

Coverage	Legal status	Approval process	Implementable standards
Time-limited points to consider that address the current needs for guidance on how GMPs should be implemented for waste and wastewater management in the production of antimicrobials	Non-binding	WHO Guidelines Review Committee	Provides expectations and interpretations of standards regarding the environmental aspects of manufacturing for the mitigation and prevention of AMR for pharmaceutical manufacturers, GMP inspectors, regulatory bodies that are responsible for environmental protection standards, and waste and wastewater management services. This mainly includes a risk assessment and effective waste treatment.
Guidance for the packaging of pharmaceutical products	Non-binding	WHO Guidelines Review Committee	Standards for important aspects of packaging for antimicrobial use and, specifically presentation and information, including labelling. Does not address antimicrobial use AMR specifically.
Guidelines for registration of fixed-dose combination medicinal products covering antimicrobials and antimicrobial resistance	Non-binding	WHO Guidelines Review Committee	Guidance only for fixed-dose combinations that reduce creation of resistance
A manual based on guidelines for marketing authorization of pharmaceutical products focusing on multisource products	Non-binding	WHO Guidelines Review Committee	Standards for good regulatory practice and quality management. Does not specifically address antimicrobial use or AMR.
Guidance on variations to multisource pharmaceutical products, focusing on establishing national requirements for the regulation of post-approval changes	Non-binding	WHO Guidelines Review Committee	Standards for an authorized multisource pharmaceutical product regarding procedures and criteria for the appropriate categorization and reporting of changes and post-approval variations to a finished pharmaceutical products. While these standards are important for antimicrobials and AMR, the instrument does not provide specific standards for antimicrobials.
Provides a procedure that allows for enhanced timely access to WHO prequalified products in countries through exchange of regulatory information	Non-binding	WHO Guidelines Review Committee	Principles and steps of collaboration and procedures for the national registration of a prequalified product when using the collaborative procedure between WHO and national regulatory authorities.
Guidance on interchangeability of multisource products	Non-binding	WHO Guidelines Review Committee	Standards for various types of equivalence studies and testing for the interchangeability of multisource products. Applies to and is important for antimicrobials and AMR, but offers no specific standards in this regard.
Provides a procedure that allows for enhanced timely access in countries to products approved by stringent regulatory authorities through exchange of regulatory information	Non-binding	WHO Guidelines Review Committee	Steps and standards for the collaboration scheme WHO proposes between national regulatory authorities and pharmaceutical manufacturers to facilitate registrations of vaccines and pharmaceutical products, including biotherapeutic products approved by reference stringent regulatory authorities.

	Name	Last updated	Type	Organization
3. Selection, procurement and supply 	Guideline on good distribution practices for pharmaceutical products (Annex 5, WHO Technical Report Series, No. 957)	2010	Guideline	WHO
	Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (Annex 9, WHO Technical Report Series, No. 961)	2011	Guideline	WHO
	Model quality assurance system for procurement agencies (Annex 3, WHO Technical Report Series, No. 986)	2014	Guideline	WHO
	Guidelines on import procedures for pharmaceutical products (Annex 5, WHO Technical Series, No. 1019)	2019	Guideline	WHO
	Model list of essential medicines (WHO essential medicines list [EML]) (21st edition)	2019	Classifi-cation	WHO
	Guideline on good storage and distribution practices for medical products (Annex 7, WHO Technical Report Series, No. 1025)	2020	Guideline	WHO
4. Appropriate and prudent use 	Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services	2011	Guideline	FIP/ WHO
	Pocket book of hospital care for children: guidelines for the management of common childhood illnesses (2nd edition)	2013	Guideline	WHO
	Guidance for national tuberculosis programmes on the management of tuberculosis in children	2014	Guideline	WHO

Coverage	Legal status	Approval process	Implementable standards
Guidance for distribution practices, focusing on the storage, sale and distribution of pharmaceutical products	Non-binding	WHO Guidelines Review Committee	Standards for the distribution of pharmaceutical products, with a particular focus on standards for regulation, management, personnel, warehouses and storage, transportation, repackaging and relabelling, recalls, returned products and counterfeit products. Provides no specific standards for antimicrobials or AMR.
Guidelines for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products	Non-binding	WHO Guidelines Review Committee	Standards for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products, including importation, storage, transport, labelling, stock management and environmental management. Provides no specific standards for antimicrobials or AMR.
An updated model quality assurance system for procurement agencies	Non-binding	WHO Guidelines Review Committee	Standards for a model quality assurance system, including the requirements for procurement agencies, pre-qualification, purchasing, storage, distribution and reassessment. Provides no specific standards for antimicrobials or AMR.
Guidance on importing pharmaceutical products	Non-binding	WHO Guidelines Review Committee	Standards for the importation of pharmaceuticals, including legal responsibilities of different actors, legal basis of control, documentation and controls. Provides no specific standards for antimicrobials or AMR.
A list of therapeutic medicines that satisfy the priority health-care needs of the global population	Non-binding	WHO Guidelines Review Committee	Guidance for the national EMLs. The WHO essential medicines list includes antibiotics (with Access, Watch, Reserve classification) and specific categories for TB, MDR-TB and antifungals.
Guidance for the storage and distribution of medical products	Non-binding	WHO Guidelines Review Committee	Standards for the storage and distribution of medical products, including steps to avoid the introduction of substandard and falsified products into the market. Provides no specific standards for antimicrobials or AMR.
Minimal standards for good pharmacy practice	Non-binding	WHO Guidelines Review Committee	Standards for good pharmacy practice. Sets as a minimal national activity that pharmacists should be proactive in AMR by providing information about the appropriate use of antimicrobials to consumers and prescribers.
A compendium of WHO guidelines and recommendations for major causes of childhood mortality in most developing countries for care in first-level referral hospitals	Non-binding	WHO Guidelines Review Committee	Guidelines for all most common infections, including neonatal infections, pneumonia, diarrhoea, ear infections, etc. In relation to the treatment of these diseases, the guideline provides standards for use of antimicrobials.
Guidelines for programmatic management of TB in children, covering diagnosis and treatment	Non-binding	WHO Guidelines Review Committee	Guidelines for the diagnosis, treatment, prevention and management of TB in children. In relation to treatment, the guideline provides standards for the use of antimicrobials and prevention of AMR.

	Name	Last updated	Type	Organization
4. Appropriate and prudent use Cont.	Revised WHO classification and treatment of childhood pneumonia at health facilities	2014	Guideline	WHO
	Guidelines for treatment of drug-susceptible tuberculosis and patient care	2017	Guideline	WHO
	AWaRe classification of antibiotics for evaluation and monitoring of use	2019	Classifi-cation	WHO
5. Disposal by the end user 	Safe management of wastes from health-care activities (2nd edition)	2014	Handbook	WHO

	Coverage	Legal status	Approval process	Implementable standards
	Guidelines for childhood pneumonia at health facilities	Non-binding	WHO Guidelines Review Committee	Guidelines for the classification and treatment of childhood pneumonia at health facilities. As part of the guidelines for treatment, standards are given for the use of antimicrobials.
	Treatment policy recommendations on priority areas in the treatment of drug-susceptible TB and patient care	Non-binding	WHO Guidelines Review Committee	Various guidelines for the treatment of drug-susceptible TB using antimicrobials
	Classifies 80 antibiotics as Access, Watch or Reserve, their pharmacological classes, Anatomical Therapeutic Chemical (ATC) codes and WHO essential medicines list status	Non-binding	Based on the WHO Expert Committee on Selection and Use of Essential Medicines	Classification of antibiotics into three stewardship groups – Access, Watch, Reserve – to guide access and responsible use of antibiotics.
	Guidance on safe waste-management practices for health-care activities	Non-binding	Based on the work of an expert group and developed by the WHO Secretariat	Standards and best practices for safe waste-management practices for health-care activities, including some best practices for mitigating and preventing AMR. Specifically stipulates that antibiotics or cytotoxic drugs should not be discharged into municipal sewers or watercourses.

Annex II: List of international instruments on the use of antimicrobials across the animal sector

	Name	Last updated	Type	Organization
1. Production 	Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)*	2005	Standard	FAO/WHO Codex Alimentarius (Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF))
	Terrestrial Animal Health Code*	2019	Standard	OIE
	Aquatic Animal Health Code*	2019	Standard	OIE
2. Market authorization and regulatory approval 	GL6 Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – phase 1	2000	Guideline	VICH
	GL38 Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – phase 2	2004	Guideline	VICH
	GL27 Pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance	2004	Guideline	VICH
	Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)*	2005	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
	GL36(R2) Studies to evaluate the safety of residues of veterinary drugs in human food: general approach to establish a microbiological ADI	2019	Guideline	VICH

Coverage	Legal status	Approval process	Implementable standards
Guidance for the responsible and prudent use of antimicrobials in food-producing animals	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	Framework for quality control of antimicrobials and assessment of efficacy. Also provides a framework for a foodborne AMR risk profile, including the requirement to have GMP and some specific additional standards for GMP.
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Calls for good manufacturing practices specifically for AMR, especially in relation to quality control
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in aquatic animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Calls for GMP in general
Standards for EIAs for VMPs excluding biologicals for Phase 1	Non-binding	Approved by the VICH Steering Committee	Standards for Phase 1 EIAs for VMPs, focusing on use in terrestrial and aquatic animals
Standards for EIAs for VMPs excluding biologicals for Phase 2	Non-binding	Approved by the VICH Steering Committee	Standards for Phase 2 EIAs for VMPs, focusing on use in terrestrial and aquatic, intensively reared and pastural animals
Guidance for registration of antimicrobial veterinary medicinal products intended for use in food-producing animals	Non-binding	Approved by the VICH Steering Committee	Standards for registration of antimicrobials, including test data for minimum inhibitory concentration tests, on resistance mechanisms and genetics, and on occurrence of resistance and cross-resistance as well as pharmacokinetic data
Guidance for the responsible and prudent use of antimicrobials in food-producing animals	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	A framework for quality control of antimicrobials and assessment of efficacy. Also provides a framework for a foodborne AMR risk profile, including marker authorization, labelling, guidelines for disposal and control of advertising.
Guidance for assessing the human food safety of residues from veterinary antimicrobial drugs	Non-binding	Approved by the VICH Steering Committee	Standards for assessing food safety of residues from veterinary antimicrobial drugs, along with options for various tests

	Name	Last updated	Type	Organization
2. Market authorization and regulatory approval Cont.	Terrestrial Animal Health Code*	2019	Standard	OIE
	Aquatic Animal Health Code*	2019	Standard	OIE
3. Selection, procurement and supply 	Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)*	2005	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
	Guidelines for risk analysis of foodborne antimicrobial resistance (CXG 77-2011)	2011	Standard	FAO/WHO Codex Alimentarius (Ad hoc Codex Inter-governmental Task Force on Antimicrobial Resistance)
	Terrestrial Animal Health Code*	2019	Standard	OIE
	Aquatic Animal Health Code*	2019	Standard	OIE
	DRAFT REVISION Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)	Ongoing	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
4. Appropriate and prudent use 	Code of practice on good animal feeding (CAC/RCP 54-2004)	2004	Standard	FAO/WHO Codex Alimentarius (Task Force on Animal Feeding (TFAF))
	Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)*	2005	Standard	FAO/WHO Codex Alimentarius (CCRVDF)

Coverage	Legal status	Approval process	Implementable standards
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Standards for market authorization and quality control in relation to AMR, including labelling and good advertising practices
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in aquatic animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Minimal standards for market authorization and quality control in relation to AMR
Guidelines for the responsible and prudent use of antimicrobials in food-producing animals	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	A framework for quality control of antimicrobials and assessment of efficacy. Also provides a framework for a foodborne AMR risk profile, including the distribution of antimicrobial agents.
Guidelines for risk analysis for foodborne AMR related to non-human use of antimicrobial agents	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	A comprehensive framework for foodborne AMR analysis and for the development of an AMR risk profile.
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Standards for wholesale and retail distributors in relation to AMR, including the stipulation that the antimicrobial label or packaging specify instructions for disposal
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in aquatic animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Standards for wholesale and retail distributors in relation to AMR, including the stipulation that the antimicrobial label or packaging specify instructions for disposal
Guidelines for the responsible and prudent use of antimicrobials in food-producing animals and plants	Non-binding (reference organization for the WTO/SPS Agreement)	To be adopted by the Codex Alimentarius Commission	The 2005 Code will be updated in the near future. The current draft is close to finalization and notably includes plant use of antimicrobials and a section on the food production environment.
Guidelines to establish a feed safety system for food-producing animals which covers the entire food chain, taking into account relevant aspects of animal health and the environment in order to minimize risks to consumers' health	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	The code of practice states that antibiotics should not be used in feed for growth-promoting purposes in the absence of a public health safety assessment.
Guidelines for the responsible and prudent use of antimicrobials in food-producing animals	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	A framework for quality control of antimicrobials and assessment of efficacy. Also provides a framework for a foodborne AMR risk profile, including the responsibilities of veterinarians and producers, and their education.

	Name	Last updated	Type	Organization
4. Appropriate and prudent use Cont.	Guidelines for the design and implementation of national regulatory food safety assurance programmes associated with the use of veterinary drugs in food-producing animals (CXG 71-2009)	2009	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
	Guidelines on use of medically important antimicrobials in food-producing animals	2017	Guideline	WHO
	Maximum residue limits (MRLs) and risk management recommendations (RMRs) for residues of veterinary drugs in foods (CX/MRL2-2018)	2018	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
	Terrestrial Animal Health Code*	2019	Standard	OIE
	Aquatic Animal Health Code*	2019	Standard	OIE
	OIE List of antimicrobial agents of veterinary importance	2019	Classifi-cation	OIE
	Prudent and efficient use of antimicrobials in pigs and poultry	2019	Manual	FAO
	Critically important antibiotics for human medicine (WHO CIA list) (6th edition)	2019	Classifi-cation	WHO

Coverage	Legal status	Approval process	Implementable standards
Guidelines for the design and implementation of national and trade-related food safety assurance programmes for residues of veterinary drugs	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	A framework for safety assurance programmes for residues
Guidelines on use of medically important antimicrobials in food-producing animals	Non-binding	WHO guidelines are approved by its Guidelines Review Committee	Guidelines recommending an overall reduction in the use of medically important antimicrobials in animals, and complete restriction of their use as growth promotors and of their preventive use in the absence of disease
MRLs for residues in foods and RMRs for residues of veterinary drugs in food	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	MRLs for residues in foods and RMRs; MRL and RMR lists include antimicrobials
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Recommendations on controlling AMR (Chapter 6.7), use and resistance monitoring programmes (Chapters 6.8 and 6.9), principles for responsible and prudent use of antimicrobials (Chapter 6.10), as well as risk analysis for AMR arising from the use of antimicrobials in animals (Chapter 6.11).
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in aquatic animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	A chapter on AMR, with an introduction to recommendations for controlling AMR (Chapter 6.1), principles for responsible and prudent use of antimicrobials (Chapter 6.2), surveillance and resistance monitoring programmes (6.3 and 6.4), and risk analysis for AMR arising from the use of antimicrobial agents in aquatic animals (Chapter 6.5)
Criteria to rank antimicrobials according to their relative importance in animal medicine and includes recommendations on use	Non-binding (reference organization for the WTO/SPS Agreement)	Prepared and reviewed by the OIE AMR Working Group; endorsed by the OIE General Session	Classification of antimicrobials of veterinary importance into three categories: important, highly important and critically important. Special recommendations are given for fluoroquinolones, cephalosporins and colistin.
Instructions for the prudent and efficient use of antimicrobials in pigs and poultry, including prevention of infections, use of antimicrobials and combining prudent use with preventive measures for good productivity	Non-binding	Reviewed by FAO	Chapter 3 focuses on effective and prudent use and provides six main action points regarding prudent and effective use of antimicrobials, including phasing out use as growth promotors and avoiding mass preventive use, taking into account the WHO CIA list and the OIE list, individual treatment based on proper diagnosis by trained veterinarians or other authorized professionals, quality pharmaceuticals and proper disposal.
Provides a ranking of medically important antimicrobials for risk management of antimicrobial resistance due to non-human use	Non-binding	Adopted by the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance	A reference to help formulate and prioritize risk assessment and risk management strategies to mitigate human health risks associated with antimicrobial use in food-producing animals. Divides antibiotics into three categories: important, critically important and highly important.

	Name	Last updated	Type	Organization
4. Appropriate and prudent use Cont.	Aquaculture development. 8. Recommendations for prudent and responsible use of veterinary medicines in aquaculture	2019	Guideline	FAO
	Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)*	2005	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
5. Disposal by the end user 	Terrestrial Animal Health Code*	2019	Standard	OIE
	Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)*	2005	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
	Terrestrial Animal Health Code*	2019	Standard	OIE

*Owing to their broad coverage of the use of antimicrobials, some documents are spread over different categories to provide the proper granularity.

Coverage	Legal status	Approval process	Implementable standards
Guidelines are intended to provide general advice in support of the implementation of FAO's Code of Conduct for Responsible Fisheries (FAO, 1995)	Non-binding	Reviewed by FAO	The recommendations set broad standards for veterinary medicines and antimicrobials. Chapter 4 specifies recommendations for the prudent and responsible use of veterinary medicines in aquaculture. The main recommendation asserts that appropriate use of antimicrobial agents and other veterinary medicines in aquaculture production is a clinical decision that should be made based on the experience and local expertise of the prescribing aquatic animal health professional.
Guidelines for the responsible and prudent use of antimicrobials in food-producing animals	Non-binding (reference organization for the WTO/SPS Agreement)	Adopted by the Codex Alimentarius Commission	A framework for quality control of antimicrobials and assessment of efficacy, together with a framework for a foodborne AMR risk profile, including an assessment of environmental impact. The code of practice also requires veterinarians and producers to follow the disposal guidance on the label.
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Requires veterinarians and producers to follow the disposal guidance on the label.
Guidance for the responsible and prudent use of antimicrobials in food-producing animals	Non-binding (reference organization for the WTO/SPS Agreement	Adopted by the Codex Alimentarius Commission	Framework for quality control of antimicrobials and assessment of efficacy. Also provides a framework for a foodborne AMR risk profile, including the requirement to have GMPs and some specific additional standards for GMP.
Standards for improving animal health and welfare and veterinary public health worldwide, including through standards for safe international trade in terrestrial animals	Non-binding (reference organization for the WTO/SPS Agreement)	Endorsed by the OIE General Session	Calls for GMPs specifically for AMR, especially in relation to quality control.

Annex III: List of international instruments on the use of antimicrobials across the plant sector

	Name	Last updated	Type	Organization
1. Production 	International code of conduct on pesticide management*	2014	Standard	FAO/WHO
	Guidelines on pesticide legislation*	2015	Guideline	FAO/WHO
2. Market authorization and regulatory approval 	International code of conduct on pesticide management*	2014	Standard	FAO/WHO
	Guidelines on pesticide legislation*	2015	Guideline	FAO/WHO
	Globally harmonized system of classification and labelling of chemicals (GHS or "the Purple Book") (8th revised edition)	2019	Guideline	United Nations (UN) Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System (GHS) of Classification and Labelling of Chemicals
3. Selection, procurement and supply 	Guidelines on pesticide advertising	2010	Guideline	FAO/WHO

Coverage	Legal status	Approval process	Implementable standards
Guidance for pesticide management, including the production, regulation and management of pesticides	Non-binding	Guidelines approved by FAO and WHO	Basic guidelines for pesticide management, including manufacturing
Guidelines, based on the International Code of Conduct on Pesticide Management, providing a model with all the elements that should be part of national pesticide laws based on international standards	Non-binding	Guidelines approved by FAO and WHO	Same standards as the International Code of Conduct on Pesticide Management and specifically emphasizes licensing of manufacturers
Guidance for pesticide management, including the production, regulation and management of pesticides	Non-binding	Guidelines approved by FAO and WHO	Basic guidelines for pesticide management, including registration and regulatory and technical requirements
Guidelines, based on the International Code of Conduct on Pesticide Management, providing a model with all the elements that should be part of national pesticide laws based on international standards	Non-binding	Guidelines approved by FAO and WHO	A framework for national pesticide laws, including administration, registration, licensing, packaging, labelling, use, advertising, storage, transport and disposal. Also proposes legislation for monitoring. Currently includes no standards specifically relating to antimicrobial use.
The GHS is an international set of rules for the classification, labelling and packaging of chemicals	Non-binding	Guidelines created and updated by the Committee of Experts on the Transport of Dangerous Goods and on the Globally Harmonized System of Classification and Labelling of Chemicals and the Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals with support from the United Nations Economic Commission for Europe (UNECE)	Provides rules for labelling in case of human or environmental danger. Currently includes no standards specifically relating to antimicrobial use.
Guidelines, based on the International Code of Conduct on Pesticide Management, covering advertising of pesticides	Non-binding	Guidelines approved by FAO and WHO	Stipulates that advertising should be legal, decent, honest and truthful, and should follow generally accepted standards of environmentally responsible behaviour. Advertising should not appear to approve or encourage actions that contravene or infringe national laws or regulations, or appear to approve or encourage non-observance of standards or self-regulatory codes.

	Name	Last updated	Type	Organization
3. Selection, procurement and supply Cont.	International code of conduct on pesticide management*	2014	Standard	FAO/WHO
	Guidelines on good labelling practice for pesticides	2015	Guideline	FAO/WHO
	DRAFT REVISION Code of practice to minimize and contain antimicrobial resistance (CXC 61-2005)	Ongoing	Standard	FAO/WHO Codex Alimentarius (CCRVDF)
4. Appropriate and prudent use 	International code of conduct on pesticide management*	2014	Standard	FAO/WHO
	Codex pesticides residues in food online database	2019	Standard	FAO/WHO Codex Alimentarius (Codex Committee on Pesticide Residues (CCPR))
5. Disposal by the end user 	International code of conduct on pesticide management*	2014	Standard	FAO/WHO
	Environmental management tool kit for obsolete pesticides – Volume 1, Volume 2, Volume 3, Volume 4, Volume 5, and Volume 6	Respectively, 2009, 2009, 2011, 2011, 2020 and 2020	Guideline	FAO

*Owing to their broad coverage of the use of antimicrobials, some documents are spread over different categories to provide the proper granularity.

Coverage	Legal status	Approval process	Implementable standards
Guidance for pesticide management, including the production, regulation and management of pesticides	Non-binding	Guidelines approved by FAO and WHO	Basic guidelines for pesticide management, including distribution and trade, information exchange, labelling, packaging, storage, and disposal and advertising
Guidelines, based on the International Code of Conduct on Pesticide Management, covering the use of all pesticides, as defined in the Code of Conduct, in any form that is destined to be applied by end users, except pesticides which are used as human pharmaceuticals	Non-binding	Guidelines approved by FAO and WHO	Directions for labelling and shows how labelling can impact use, public health and environmental hazards, but currently does not specifically focus on antimicrobial use. With respect to health hazards, the guideline relies on the WHO classification of pesticides by hazard, which deals only with acute risk to human health.
Guidelines for the responsible and prudent use of antimicrobials in food-producing animals and plants	Non-binding (reference organization for the WTO/SPS Agreement)	To be adopted by the Codex Alimentarius Commission	The 2005 Code will be updated in the near future. The current draft is close to finalization and notably includes plant use of antimicrobials and a section on the food production environment.
Guidance for pesticide management, including the production, regulation and management of pesticides	Non-binding	Guidelines approved by FAO and WHO	Basic guidelines for pesticide management regarding availability and use and monitoring
The database contains the Codex Maximum Residue Limits for Pesticides and Extraneous Maximum Residue Limits adopted by the Codex Alimentarius Commission up to and including its 42nd session (July 2019).	Non-binding	Adopted by the Codex Alimentarius Commission	Sets limits for various fungicides or other pesticides with antimicrobial effects
Covers pesticide management, including the production, regulation and management of pesticides	Non-binding	Guidelines approved by FAO and WHO	Basic guidelines for pesticide management, including disposal. Provides no specific standards for antimicrobials.
Toolkit, based on the International Code of Conduct on Pesticide Management, giving guidelines for management of obsolete pesticides	Non-binding	Guidelines approved by FAO	Deals very broadly with the management of obsolete pesticides, but not specifically antimicrobials

Annex IV: Questions in TrACSS 4.0 (2019–2020) regarding standards on the use of antimicrobials

The 2019–2020 (TrACSS 4.0) survey contained several questions regarding standards on the use of antimicrobials:

Question 5.4 whether a county has laws and regulations in place "on the prescription and sale of antimicrobials for human use", "on prescription and sale of antimicrobials for animal use", "that prohibit the use of antibiotics for growth promotion in the absence of risk analysis" and "on the marketing of pesticides, including antimicrobial pesticides, such as bactericides and fungicides used in plant production".

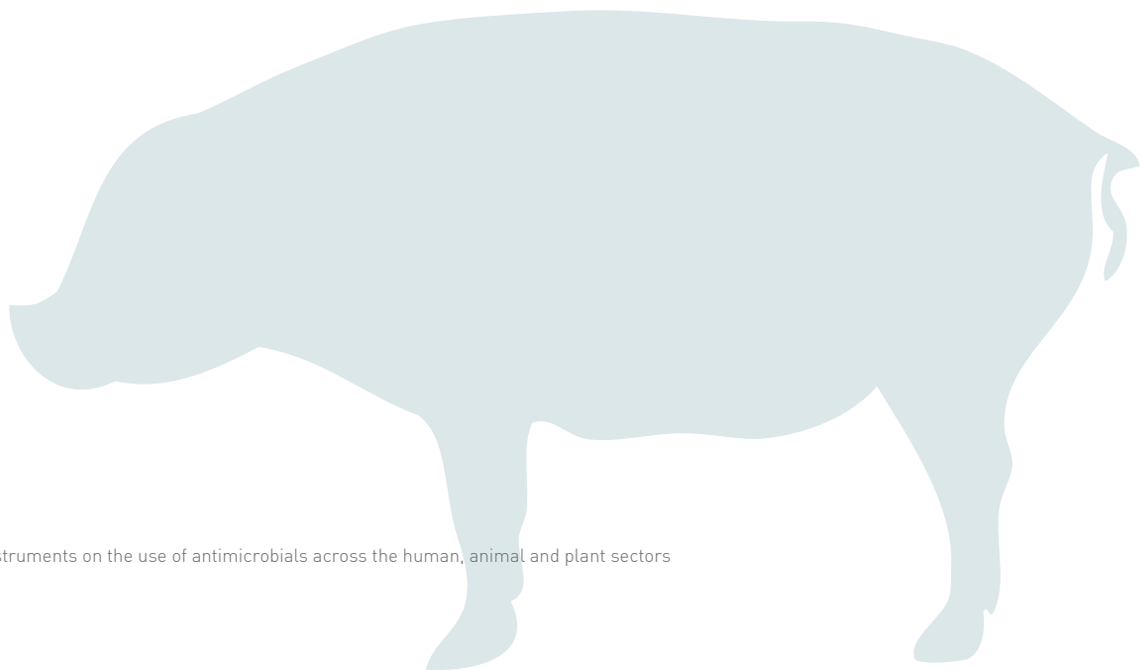
Question 6.5 on country progress in strengthening their veterinary services.

Questions 7.1, 7.2 and 7.3 respectively, on monitoring the use of antimicrobials in the human, animal and plant sectors.

Questions 9.1 and 9.1.1 respectively, on policies for optimizing use in humans and implementing the WHO AWaRe classification.

Questions 9.2 and 9.3 respectively, on actions and policies for optimizing use in animals and plants.

Question 10 covers legislation and regulation to prevent contamination of the environment with antimicrobials including discharge and disposal.



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