

# Antimicrobial resistance and the standards of the World Organisation for Animal Health

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## Summary

Antimicrobial resistance and the use of antimicrobial agents in veterinary medicine are complex issues that are currently a source of major international concern.

It is therefore essential for the World Organisation for Animal Health (OIE) to consider this issue, while at the same time continuing to address the problem of zoonotic diseases. That is why the OIE has included objectives for veterinary drugs, especially antimicrobials, in its Strategic Plan.

The OIE plays an active part in discussions on this subject in conjunction with other international organisations working in this field, such as the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). Furthermore, the OIE has adopted guidelines both for defining harmonised methodologies for antimicrobial resistance surveillance and monitoring and for helping countries to conduct a risk analysis tailored to their situation and to take appropriate management measures.

The OIE has included this issue in its programme of assistance to countries by offering them structural enhancement tools: the Tool for the Evaluation of Performance of Veterinary Services (OIE PVS Tool), PVS Gap Analysis, veterinary legislation support, and training for veterinary national focal points, with the aid of its Collaborating Centres for veterinary medicinal products.

Only by mobilising all countries to improve the quality of antimicrobials, to introduce antimicrobial resistance surveillance and to implement measures for the responsible and prudent use of antimicrobials, will it be possible to halt the spread of antimicrobial resistance.

## Keywords

Antimicrobial agent – Antimicrobial resistance – Guidelines – International – Responsible use – Standard – World Organisation for Animal Health.

## Introduction

Animal health and human health are closely linked because of the existence of a large number of zoonotic diseases and the impact of unhealthy livestock on human food. The World Organisation for Animal Health (OIE) has therefore helped to develop the 'One Health' concept and focused its strategic policy on the need to ensure animal health and welfare worldwide.

Veterinary medicinal products are considered essential to ensuring animal health and welfare and to improving

public health in general. Livestock producers and animal health professionals in the field need fast access to good quality, safe and effective veterinary medicinal products at a reasonable price. This is crucial to ensuring the health of livestock and hence to limiting epizootics. This, in turn, helps to prevent the transmission of diseases such as zoonoses to humans through contact with animals or their environment, through a vector or by consuming food of animal origin.

While this applies to all countries, it is of particular importance in developing countries, which all too often

have neither sufficient resources nor the conditions for securing a supply of effective veterinary medicinal products.

This makes it essential for national authorities to create the necessary conditions, in particular by implementing a strict and clearly defined policy for veterinary medicinal products. Protecting animal health and human food security, by ensuring a healthier herd, will also contribute to economic development and poverty reduction.

Antimicrobials are vital drugs because they are key in treating and controlling infectious diseases in both humans and animals. However, the use of antimicrobials (to treat humans, animals and plants) has led to the development of resistance, which is of increasing concern, mainly because no new antimicrobial molecules are being discovered.

Antimicrobial resistance is a global phenomenon that respects no species barriers and has become a leading animal health concern in the same way as certain zoonotic diseases.

Public policy on veterinary medicinal products is therefore an ongoing concern for the OIE and is a fully-fledged component of animal health policies. As the more specific problem of antimicrobial resistance has become a threat to human and animal health, the OIE has also defined international recommendations for preventing the spread of resistance. The OIE's general strategy, described in its Fifth Strategic Plan for 2011–2015, addresses this concern.

## General strategy of the OIE, a major international player

Over the past 20 years, the main topics of international debate have been: surveillance of antimicrobial consumption and resistance in veterinary medicine, risk analysis and the prudent use of antimicrobials.

Between 1990 and 2000, OIE activities focused mainly on drawing up guidelines (see the section on standards in the OIE *Terrestrial Animal Health Code [Terrestrial Code]*). However, since 2003 and in recent years the trend has changed. While the OIE has continued to work on setting and updating guidelines, it has begun to consider issues concerning their implementation.

The foundations for current activities were laid mainly by two joint meetings of the Food and Agriculture Organization of the United Nations (FAO), the OIE and the World Health Organization (WHO) on non-human antimicrobial usage and antimicrobial resistance, held in Geneva in 2003 and Oslo in 2004. Three main directions emerged from the two meetings:

- the need to progress with the concept of risk analysis in the area of antimicrobial resistance
- the idea of establishing lists of critically important antimicrobials in human and veterinary medicine
- the need for capacity building, networking and coordination to facilitate the implementation of surveillance programmes.

### Risk analysis

One of the recommendations of the 2004 joint FAO/OIE/WHO meeting in Oslo was to set up a Codex Alimentarius (Codex) Intergovernmental Task Force on Antimicrobial Resistance (TFAMR) jointly with the OIE to develop risk-management options for antimicrobial resistance arising from non-human antimicrobial use. The aim of the Codex Task Force was to develop risk assessment guidelines on foodborne antimicrobial resistance to take into account the risk assessment principles and standards of other international organisations such as the OIE, FAO and WHO.

After meeting four times, the Task Force adopted guidelines at its latest meeting in late 2010, which the Codex Alimentarius Commission validated in July 2011 (1).

### The concept of critically important antimicrobials

Another recommendation of the joint FAO/OIE/WHO meeting in Oslo was that the WHO should develop the concept of critically important classes of antimicrobials for humans with a view to implementing specific resistance-preventive activities for these antimicrobials in the context of non-human use. It also recommended that the OIE should develop a list of critically important classes of antimicrobials for animals. The WHO established a list of critical antimicrobials for human medicine at two expert meetings, held in Canberra in 2005 and Copenhagen in 2006. This list was amended slightly in 2009 and again in 2011 at meetings of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR) (2).

The OIE, through its *Ad Hoc* Group on Antimicrobial Resistance, proposed a definition of the concept of veterinary critically important antimicrobials in 2005 and sent a questionnaire on the subject to all OIE Member Countries.

A draft list of antimicrobials of veterinary importance was adopted in May 2006 and a final revised list was adopted in May 2007 (3).

A further joint FAO/WHO/OIE meeting was held in Rome in November 2007 to revise the two lists.

While the goal of the Oslo meeting was to draw up these lists in order to implement preventive measures, the conclusions of the Rome meeting were very different. The Rome meeting recommended that the WHO and OIE lists of critically important antimicrobial agents should be considered when prioritising drug/animal species/pathogen combinations for risk assessment. Methodologies for setting risk-assessment priorities were proposed for this purpose and the meeting called for the emphasis to be placed on cephalosporins, fluoroquinolones and macrolides, in particular for *Salmonella* spp., *Campylobacter* spp. and *Escherichia coli*.

### Country capacity building

Most of the international meetings recommended building the capacity of countries to control antimicrobial resistance.

The OIE has led discussions in this area and set up a programme to evaluate the capacity of Veterinary Services. A resolution to this effect was adopted in May 2009, providing for measures to be introduced in the field of veterinary medicinal products, in particular antimicrobial resistance. A number of international conferences and training courses have been held or are planned.

In 2008, the WHO set up the AGISAR Advisory Group to implement specific projects on antimicrobial resistance arising from the use of antimicrobials in food animals.

### OIE Fifth Strategic Plan

In response to this comprehensive global approach, the OIE has enshrined in its 2010 Fifth Strategic Plan a strong commitment to strengthen collaboration with FAO and WHO (in particular via the Codex Alimentarius Commission) and supports the work of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH):

‘In the area of veterinary drugs, including antimicrobials, the Laboratories Commission will strengthen its liaison with the Codex Committee on Residues of Veterinary Drugs in Foods and the ad hoc Codex Intergovernmental Task Force on Antimicrobial Resistance. The Commission will seek to extend the coverage of the programme on International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) to all OIE Members by encouraging the OIE to adopt, if possible, parallel standards proposed by VICH. Delegates to the OIE have nominated a Focal Point for Veterinary Drugs and Vaccines.’

## Standards in the OIE *Terrestrial Animal Health Code:* an aid to Member Countries in implementing an antimicrobial resistance prevention and reduction policy

To assist its Members in implementing the strategic objectives set out above, the OIE has adopted a number of guidelines, most of which are included in the *Terrestrial Code*, as well as the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Terrestrial Manual)* and the *Aquatic Animal Health Code (Aquatic Code)*. These standards are used to define a harmonised framework for managing veterinary medicinal products and for antimicrobial resistance surveillance and monitoring, which are prerequisites for developing risk analysis and for adopting management measures and recommendations tailored to each country's specific requirements.

### Guidelines on surveillance and monitoring

#### Harmonisation of national antimicrobial resistance surveillance and monitoring programmes (Chapter 6.7. of the *Terrestrial Code*)

Regular surveillance of antimicrobial resistance, and its development in pathogenic and non-pathogenic bacteria found in animals, food of animal origin or the environment, constitutes a critical part of any strategy aimed at limiting the spread of antimicrobial resistance. Resistance surveillance is also used to optimise the choice of antimicrobials for treating animals and to make recommendations to veterinary prescribers.

Accordingly, in May 2003, the OIE adopted guidelines on the harmonisation of national antimicrobial resistance surveillance and monitoring programmes in animals and in food of animal origin intended for human consumption (5). The main objective of these guidelines is to provide criteria for developing national antimicrobial resistance surveillance and monitoring programmes or for harmonising existing ones.

Such surveillance is used to follow trends in antimicrobial resistance in bacteria, detect the emergence of new antimicrobial resistance mechanisms and provide the data necessary for conducting risk analyses with relevance for human and animal health. These data then inform the recommendations made to prescribers for prudent antimicrobial use.

The guidelines define a sampling strategy with recommendations on:

- sample source (animal, food, animal feed)
- categories of bacteria to be monitored
- classes of antimicrobials to be used in susceptibility testing
- type of data to be recorded.

It is important to conduct such surveillance over time in order to study trends and take appropriate management measures.

#### **Laboratory methodologies for bacterial antimicrobial susceptibility testing (Chapter 1.1.6. of the *Terrestrial Manual*)**

These guidelines enable laboratories to determine which *in vitro* antimicrobial susceptibility testing (AST) methodology to use (4). It is imperative for the different laboratories to use a similar procedure to determine their AST methodology, as well as harmonised and standardised procedures for interpreting the results.

Such standardisation of AST methodology and of results interpretation allows for a direct comparison of results between different countries or even regions.

#### **Monitoring of the quantities of antimicrobials used in animal husbandry (Chapter 6.8. of the *Terrestrial Code*)**

The main purpose of these guidelines is to define the approach to be used for collecting objective and quantitative information to evaluate antimicrobial usage patterns in animal production, by animal species and antimicrobial class (6), in order to evaluate antimicrobial exposure.

The information provided in these guidelines can be helpful in interpreting antimicrobial resistance surveillance data and in responding to resistance problems in a more precise and targeted way by implementing mitigation strategies tailored to the situations encountered. The information may also assist in evaluating the effectiveness of any measures adopted.

The basic data collected should be the annual weight in kilograms of the active ingredient of the antimicrobial(s) used for each species, together with the type of use and route of administration. Information on dose rates and duration of treatment is important in estimating the use of antimicrobials in animals.

### **Guidelines on legislation, use of veterinary medicinal products and risk analysis**

#### **Guidelines on veterinary legislation**

Veterinary legislation is a crucial element of the national infrastructure that enables Veterinary Services to carry out their key functions efficiently in all fields of animal health, including surveillance and rapid response to, and prevention and control of, animal health emergencies. Veterinary medicinal products are therefore a vital component of veterinary legislation implementation.

At its 79th General Session in May 2011, the OIE adopted guidelines setting out recommendations for developing a regulatory framework to enable Members to introduce an effective animal health policy and endow control services with the necessary legal powers. These guidelines serve to support countries in improving the health of their livestock and complying with OIE standards (10).

Apart from making recommendations on the general legal framework, the powers of the competent authority and potential systems of penalties, these guidelines make specific recommendations regarding the minimum legislation to be introduced in each technical sector. A chapter devoted to veterinary medicine defines the main areas to be regulated throughout the veterinary medicinal product chain, ranging from marketing authorisation, to raw materials, manufacturing and distribution conditions and quality control of veterinary products.

#### **Risk assessment for antimicrobial resistance arising from the use of antimicrobials in animals (Chapter 6.10. of the *Terrestrial Code*)**

These guidelines set out a methodology enabling OIE Member Countries to establish a risk analysis for antimicrobial resistance in order to assess and manage the human and animal health risks of resistance arising from antimicrobial use in animals (8).

This risk analysis must include:

- hazard identification based on the results of surveillance
- a release assessment of resistant microorganisms or resistance determinants
- an exposure assessment of probable exposure to identified hazards
- a consequence assessment of the potential consequences of a given exposure.

All this is designed to estimate the risk and help to determine the management and risk communication measures to be undertaken.

## Responsible and prudent use of antimicrobial agents in veterinary medicine (Chapter 6.9. of the *Terrestrial Code*)

Chapter 6.9. of the *Terrestrial Code* makes recommendations directed at all stakeholders in the veterinary medicinal product chain to ensure their prudent use of antimicrobials (7).

The recommendations are intended primarily for the competent authorities in charge of establishing the regulatory framework required for assessing and authorising antimicrobials, controlling their quality and advertising and supervising their distribution and surveillance.

Recommendations are also aimed at the pharmaceutical industry, retail distributors of veterinary antimicrobial products, prescribing veterinarians and food-animal producers.

Special attention must therefore be paid to each stage of the use of antimicrobials, extending from their authorisation to their administration to animals, with specific recommendations for each stakeholder at every stage in an antimicrobial's life.

## Prospects and future work

The OIE is currently developing guidelines on resistance to antimicrobial agents used in aquaculture. The aim is to adapt the guidelines for terrestrial animals to take into account the specific characteristics of the aquaculture industry. Preliminary guidelines on the responsible and prudent use of antimicrobials in aquaculture were adopted at the 79th OIE General Session for inclusion in the *Aquatic Code* (Chapter 6.3.) (9).

An *ad hoc* group was set up to revise the current guidelines on antimicrobial resistance in the *Terrestrial Code*, which were drawn up in 2004 and 2005. A first draft was submitted to OIE Members for comment. The revision of Chapter 6.10. on risk assessment for antimicrobial resistance will take into account the results of work by the Codex Task Force (1).

## OIE tools

The OIE provides its Member Countries with a number of tools to help them to implement the antimicrobial resistance guidelines more effectively. General OIE tools include the Tool for the Evaluation of Performance of Veterinary Services (OIE PVS Tool), which enables countries to make an accurate diagnosis of their ability to

manage risk, assess their degree of implementation of OIE guidelines and identify areas for improvement. The OIE has also introduced more specific tools for veterinary medicinal products by designating Collaborating Centres for veterinary medicinal products, establishing networks of national focal points and organising training seminars.

## OIE PVS Pathway

The OIE PVS Pathway is a global programme for the sustainable improvement of the compliance of a country's Veterinary Services with OIE standards on the quality of Veterinary Services (11).

To support this objective, there is a crucial need for appropriate legislation in the animal health and welfare field and its strict implementation through appropriate human and financial resources.

The OIE international standards and guidelines form the basis for independent external country evaluations of the quality of Veterinary Services and animal health systems. A specific methodology has been developed and the OIE has published the OIE PVS Tool as the basis for evaluating performance against the international standards published in the *Terrestrial Code*.

Only OIE-certified PVS experts can carry out independent external PVS Evaluations of country Veterinary Services and PVS Gap Analysis. They have undergone training sessions organised by the OIE (funded by donors to the OIE World Animal Health and Welfare Fund). All experts use standard tools, indicators and experts' manuals (including template reports) prepared and published by OIE Headquarters.

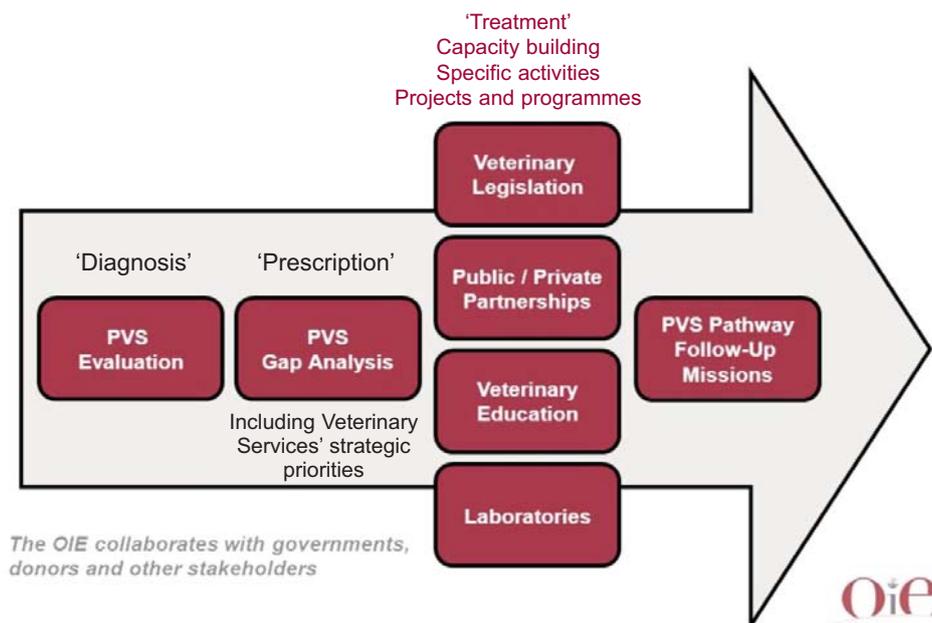
Between 2006 and 2010, the OIE progressively developed the OIE PVS Pathway. The first steps in the pathway are the country PVS Evaluation (carried out using the OIE PVS Tool) and the PVS Gap Analysis mission. Each step is integrated into a comprehensive, staged approach that provides targeted support for the systematic strengthening of Veterinary Services based on international standards.

Figure 1 is a visual representation of the OIE strategy regarding the use of OIE standards on the quality of Veterinary Services and guidelines on veterinary legislation.

## PVS Gap Analysis

The PVS Gap Analysis Tool (a 'prescription tool') is a quantitative evaluation of a country's needs and priorities (based on the outcome of the independent external evaluation of the country's Veterinary Services using the OIE PVS Tool). A series of different national factors and

## The OIE PVS Pathway



**Fig. 1**  
OIE strategy for building the capacity of Veterinary Services using the PVS (Performance of Veterinary Services) Pathway

conditions needs to be taken into consideration when shifting from the qualitative evaluation (country PVS report) to a quantitative assessment of needs and priorities (PVS Gap Analysis report).

A PVS Gap Analysis mission facilitates the definition of the objectives of a country's Veterinary Services in terms of compliance with OIE international standards on quality of Veterinary Services. Each objective must be suitably adapted to national constraints and priorities. The country PVS Gap Analysis report includes an indicative annual budget and, where relevant, an exceptional budget (for exceptional investments); these two budgets are consolidated to propose an indicative five-year budget for the Veterinary Services.

### Veterinary legislation

The ability to prepare and implement legislation are among the 46 critical competencies identified in the OIE PVS Tool.

The OIE is aware that in many developing countries veterinary legislation is outdated and inadequate for addressing current and future challenges. At the request of Members, the OIE has developed guidelines on veterinary legislation, setting out the essential elements that should be covered by legislation to meet OIE quality standards. Any country that has undergone a PVS evaluation can request a follow-up mission to obtain advice and assistance in modernising their national veterinary legislation. These

guidelines will be used to update legislation in the light of the gaps identified by the OIE PVS evaluation and must of course be tailored to each country's specific situation.

### OIE global programmes for modernising veterinary legislation

As a follow-up to a PVS evaluation, and at the request of Members, the OIE conducts missions to help governments wishing to modernise their national veterinary legislation and thereby help Veterinary Services to meet OIE standards. After an initial 'identification' mission the country may request longer-term collaboration with the OIE, under a formal agreement, with the objective of modernising the national veterinary legislation.

Veterinary legislation missions, like the other components of the PVS Pathway, are carried out by experts trained and certified by the OIE. The first OIE global conference on veterinary legislation, entitled 'Modernising veterinary legislation for good governance', took place in Djerba, Tunisia, in December 2010.

### Tools specific to veterinary medicinal products

#### Collaborating Centres for veterinary medicinal products

The OIE relies on special structures – Collaborating Centres – to provide specific expertise in a given specialty

area. Collaborating Centres help to develop and implement OIE strategic policy. Not only do Centres participate in or even run *ad hoc* expert groups responsible for setting guidelines, they also design scientific and technical training programmes for national focal points and participate in the courses.

The first Collaborating Centre for veterinary medicinal products was appointed in 1995: France's *Agence Nationale du Médicament Vétérinaire*, which has expertise in all categories of veterinary medicinal products. Since then, a further two Collaborating Centres have been appointed: Japan's National Veterinary Assay Laboratory, which has expertise in vaccines (2009), and the United States Food and Drug Administration, which has expertise in chemical drugs (2010). The addition of these new centres has enabled the formation of a network of Collaborating Centres.

### Network of national focal points and capacity-building activities

Regional programmes for building the capacity of Veterinary Services in OIE Member Countries are established annually. They promote networking between country Delegates to the OIE and national focal points.

The OIE has asked each of its Members to appoint national focal points for certain issues it considers important, including veterinary medicinal products. At its 76th General Session, the OIE reaffirmed the important role of national focal points and adopted terms of reference defining their roles and responsibilities. The permanent Delegate is the official representative of his or her Member Country in dealings with the OIE, while national focal points are specialists in the respective subject and responsible for providing expertise to the permanent Delegate, as well as acting as a key contact person for the OIE in connection with opinions or questionnaires on the subject in question.

The OIE Regional and Sub-Regional Representations organised two seminars on veterinary medicinal products: one for the Africa region, held in Dakar in 2008, and the other for the Middle East, held in Syria in 2009. The aim of these regional seminars was to develop capacity and provide Delegates and national focal points with information and in-service training on veterinary medicinal products. They were also intended to allow national focal points to get acquainted and engage in networking.

The regional seminars have now been replaced by training courses for national focal points. The first cycle of training was held in each of the five regions from July 2010 to May 2011. A second cycle began in September 2011 and is planned to conclude in 2012.

## Conclusion

Antimicrobial resistance and the use of antimicrobial agents in veterinary medicine are complex issues that are currently a source of major international concern. This concern should be taken into account and an appropriate response provided, supported by tangible results.

The main unanswered question is: how much responsibility does veterinary antimicrobial use bear for the emergence, selection and spread of resistant bacteria with the potential to infect humans? Most international reports on the subject conclude that, while antimicrobial use in humans is primarily responsible for the emergence of bacterial resistance, veterinary use of antimicrobials is also partly responsible.

It is therefore crucial that the OIE engages with this issue, while also continuing to address the problem of zoonotic diseases. That is why the OIE has included objectives for veterinary medicinal products, especially antimicrobials, in its Strategic Plan.

Consequently, the OIE plays an active part in discussions on this subject in conjunction with other international organisations such as FAO and WHO. Furthermore, the OIE has adopted guidelines both for defining harmonised methodologies for antimicrobial resistance surveillance and monitoring and for helping countries to conduct a risk analysis tailored to their situation and to take appropriate management measures.

Antimicrobial resistance is a global phenomenon that affects all countries. Clearly not all developing countries have a sufficiently developed legal system to provide a regulatory framework for veterinary medicinal products, including antimicrobials, from design to use. It is also essential for competent authorities to be endowed with competent inspection services and quality control structures in order to detect counterfeit drugs. The OIE has therefore developed recommendations and tools to help countries to improve their legislation. It has included this issue in its programme of assistance to countries by offering them structural enhancement tools – OIE PVS Tool, PVS Gap Analysis, veterinary legislation support, and training for veterinary national focal points – with the aid of the OIE network of three Collaborating Centres for veterinary medicinal products.

Only by mobilising all countries to improve the quality of antimicrobials, to introduce antimicrobial resistance surveillance and to implement measures for the responsible and prudent use of antimicrobials, will it be possible to halt the spread of antimicrobial resistance.



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