

## Antimicrobials – Protecting the future

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### Introduction

As in human medicine, the introduction from the 1940s onwards of effective antimicrobial agents for veterinary use has brought significant improvements in animal health and welfare. These medicines have provided veterinarians and animal owners with a means of treating and controlling previously intractable conditions caused by bacteria, protozoa and fungi.

Good health is the cornerstone of high welfare standards for all domestic species and for those used in food production - it is a key determinant of sustainable productivity. Supplies of wholesome, nutritious and affordable animal protein are more widely available now than ever before because fewer farm animals fail to thrive or are lost prematurely to disease. So by providing the means for improving animal health and welfare and for reducing the economic damage caused by infectious disease, antimicrobials have generated significant benefits for the whole of society. Additionally, our ability to protect the health of animals also reduces the risk of transmission of a number of zoonotic diseases that could threaten human health - human health is linked to animal health.

However, the animal health industry can – and must – make an even greater contribution to the public good by ensuring further improvements in our control of livestock disease. Globally at least 20% of animal-based food production is lost as a result of largely preventable diseases (Source: OIE). In those countries in the developing world that are most vulnerable to food shortages this wastage can be very much greater. For 700 million people across the world living in poverty, quality of life depends on their livestock's health. Animals not only provide them with crucial food protein and income but also work power in the form of traction, ploughing or irrigation and as natural fertilisers (Source: FAO).

Meanwhile, there will be further pressure to increase production of meat, fish, eggs and dairy products as the human population continues to grow. There are currently around 7 billion mouths to feed and the number will go on rising, reaching an estimated 9.3 billion by 2050 (Source: UN). Malnutrition is already widespread and so, over the next few decades it is calculated that food production will need to increase by around 100 per cent. Most land suitable for agriculture is already in use, which will mean that around 70 per cent of this increase will have to come from greater efficiency and improved farm technology. Clearly, we must do our best to prevent and control diseases in animals.

Antimicrobials are not the only item in the veterinary toolbox. There are many other factors that will influence the spread of disease on farms – and high standards of biosecurity, housing, nutrition,

disease monitoring and herd health planning will certainly reduce the risks. But ensuring the availability of effective veterinary medicines is the measure most likely to bring us closer to that distant goal of freedom from contagious disease.

Animal health companies face significant regulatory hurdles in introducing new products to a market that is many times smaller than that served by the human pharmaceutical industry. So the challenge for governments and medicines agencies is to create the economic and legal environment necessary to sustain research and innovation in veterinary medicines to further tackle animal diseases - for the sake of the animals, their owners and wider society.

## Antimicrobial resistance - Policy positions of key stakeholders

Resistance to the effects of antimicrobial agents is a natural phenomenon which may occur spontaneously within any bacterial population. However, there is considerable variation in the type of resistance seen in different situations and in the frequency with which it occurs. It is important to comply with the label conditions using the appropriate product given at the right time and at the right dose.

Given the importance of this subject for both animal and human health, and also food production, different stakeholders from both the political side and the scientific side have developed policies to tackle antimicrobial resistance.

In November 2009 a **European Commission staff working paper on antimicrobial resistance** was published. This identified the loss of efficacy of antimicrobial agents as a 'largely unresolved issue in public health', with 25,000 patients dying each year in the EU as a result of infections caused by resistant pathogens. Healthcare costs and lost productivity were estimated at more than €1.5 billion a year.

The document gave an overview of EU activities in tackling antimicrobial resistance (AMR) in human and veterinary medicine, and in other relevant areas, such as crop protection, biocides, etc. It identified areas for further action and the types of activities that could be envisaged. This paper served as a basis for consultation and discussion with the European Parliament, Member States, European scientific bodies and stakeholders.

In June 2010, the **Heads of Medicines Agencies** (HMA) published a **strategic plan on antimicrobial issues**, which highlighted the need for maintaining the efficacy of antimicrobials and minimising resistance as one of the most important tasks in veterinary medicine. However, it said any measures taken should be balanced so that the availability of necessary antimicrobial veterinary medicines is not unreasonably restricted.

The HMA argued that the responsible use of all veterinary antimicrobials should be the focus of any actions to minimise the development of AMR. It also highlighted the importance of improved communications at an international level and recognised the value of meetings held during the Czech presidency of the EU between the European Medicines Agency (EMA) and key stakeholders in coordinating and prioritising actions.

In its strategic plan, the HMA recognises the importance of all antimicrobials being classed as prescription-only medicines. It also highlighted the importance of surveys of antimicrobial consumption and resistance in both human and veterinary medicine. This information is vital both in carrying out risk assessments and in developing a communication strategy to guide users of these products.

Improved monitoring of antibiotic use at farm level was also part of the package of measures proposed by a working party of national **Chief Veterinary Officers (CVOs)** in a report giving their **conclusions on antimicrobial resistance** released in October 2010.

The report argued the importance of the strict enforcement of the existing regulatory framework against inappropriate and excessive use of these products, and particularly efforts to minimise their use as preventative treatments.

It also highlighted the importance of appropriate biosecurity to reduce the infectious load at farm level and on management strategies which promote the use of alternative methods such as vaccination to prevent infectious disease.

The CVOs' report noted the need to work with key stakeholder organisations in developing guidelines for the responsible use of antibiotic agents in different species. It also favoured efforts to discourage use of the cascade system, which allows for the prescription by veterinary practitioners of products not authorised in the target species. Improved education and training for all those involved in the management of livestock was also an important factor, along with continued research to identify possible risk factors for the emergence and selection of resistance.

In July 2011 the European Medicines Agency's **Committee for Medicinal Products for Veterinary Use (CMVP)** issued a report on its **strategy on antimicrobials 2011-2015**. This confirmed the importance of effective antimicrobial treatment for relevant indications in all species to alleviate pain and suffering.

The CMVP also wished to encourage innovation in the development of alternatives to existing antimicrobial agents. If new classes of antimicrobial agents are introduced, the committee suggests that these may be restricted to human use. However, such decisions should be made only on the basis of a risk assessment and without unnecessarily restricting the availability of medicines for veterinary use.

For existing classes of antimicrobial agents, the committee insists that these should be used in a responsible way to avoid unnecessary selection pressure for AMR. In particular, it says that fluoroquinolones and 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporin products should be classed as second line antimicrobials to be reserved for conditions that have responded poorly to other agents and should not be used for general prophylaxis in, for example, pig and poultry production.

Going beyond those recommendations, the **European Food Safety Authority (EFSA)** produced a scientific opinion in September 2011 which recommended discontinuing or restricting all use of 3<sup>rd</sup> and 4<sup>th</sup> generation cephalosporins in food-producing animals. This was proposed as a measure to stop the development and spread of two bacterial resistance mechanisms - extended spectrum beta lactamases (ESBL) and AmpC beta-lactamases.

EFSA found a significant increase in ESBL-producing strains isolated from poultry over the past decade due to the unauthorised use of cephalosporins in hatcheries. However, the scientific opinion recognised that the prevalence of resistance (i.e., the percentage of non-wild type bacterial organisms) in the two main target species, cattle and pigs, has remained ‘very low to low’ even after two decades of using these products on European farms. While prohibiting such off-label use of this class of agents in poultry may be an appropriate response to this problem, the ban in other animal species would be disproportionate.

European Union leaders have also recognised that the issue of AMR cannot be addressed by its Member States working in isolation. The expanding international trade in animals and their products and the increasing frequency of international travel both favour the potential spread of resistant bacteria between continents.

In a declaration agreed at the EU-US Summit in November 2009 it was decided to set up a “...transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare- and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs.”

The ***Transatlantic Taskforce on Antimicrobial Resistance*** (TATFAR) published its first report on 22 September 2011, which included a set of 17 recommendations for future cooperation to ensure that antimicrobials remain effective. These include the setting up of working groups to produce a common strategy on key issues and holding regular meetings between officials of the relevant authorities, such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

The European Parliament voted through Resolutions in May and October 2011 concerning antimicrobials. The emphasis on responsible use, European Platform for the Responsible Use of Medicines in Animals (EPRUMA) and innovation is welcomed and the call in the May Resolution to define appropriate prophylactic use is of value.

The European Commission launched a communication to the European Parliament and the Council entitled ‘***Action plan against the rising threats from Antimicrobial Resistance***’ on 17 November 2011. This 5-year strategy takes a holistic view, including a focus on the “One Health” approach. The references to responsible use and the One Health approach are welcomed but the clear need for innovation in the veterinary sector needs to be accepted.

## **IFAH-Europe policy recommendations**

In response to the foregoing policy initiatives, certain interest groups have made proposals which the animal health industry believes are unnecessary, impractical and likely to have damaging repercussions for animal health and welfare and undermine innovation. These include suggestions such as restricting the right of veterinarians to dispense antimicrobials and imposing special taxes to curb the use of these products. Some have also argued for the application of the precautionary principle to allow for the banning of particular products in the absence of any convincing evidence of their detrimental effects and with disregard for their positive and often unique benefit to animal health.

In contrast, as the representative body for the European animal health industry, IFAH-Europe argues strongly that any decisions with serious implications for human or animal health should be based on sound science and following an impact analysis according to the better regulation framework.

IFAH-Europe will always acknowledge the paramount importance of safeguarding public health, but would argue that this is best achieved through measures that create conditions which minimise the selection pressure that could give rise to resistant strains.

In veterinary medicine, such measures would include:

- **The strategic and responsible use of all antimicrobial products**, irrespective of which class they belong to – so these agents should never be used routinely to treat livestock or companion animals but should be given only when an animal has disease, has had close contact with other animals which have developed disease or is at a significant risk of infection.
- Wherever possible, **prescriptions of antimicrobial products should be made on the basis of the results of laboratory tests** to identify the specific pathogen strain and its susceptibility to that particular class of agents. When urgent clinical factors require the application of empirical treatment, then sampling before treatment should be performed and laboratory tests should be carried out, including bacterial culture and antimicrobial susceptibility to inform future choices of antimicrobial products.
- **The use of the ‘Cascade’ system should only be under exceptional circumstances**, in which no authorised medicines are available. In these situations, the veterinarian can, for example, use products authorised in other European countries or which have been authorised for use in other species. Products should be dispensed in strict accordance with the guidelines laid down for the Cascade, which is intended to prevent unacceptable suffering in animals.
- **Eliminating ‘off-label’ use of veterinary antimicrobials other than according to the Cascade** – i.e., their application in an indication that is not approved by the regulatory authorities including at a low dose.
- **Efforts to maintain the availability of new and existing classes, products and formulations** of antimicrobial agents are necessary. The rate of new product introductions has slowed down in recent years due in part to the economic and regulatory burdens of developing new products. **Increasing the data protection** available for new products will encourage companies to make the required investment in innovation. In addition, novel developments of existing products must also be granted appropriate data protection.
- **Support for the EU Member State Chief Veterinary Officers’ (CVOs) efforts to improve the collection of data on antimicrobial usage at farm level.** It is important to have transparency at the prescription and use phase. This may best be achieved by working with the veterinarians to ensure that appropriate records are available in a manner that delivers transparency. Such information will help to ensure that policy decisions are based on accurate, up-to-date evidence, that any actions can be made in a timely fashion and that the efficacy of such actions can be assessed. Importantly, this information will reassure all parties concerned that antimicrobials are being used according to responsible use patterns representing good practice.

## IFAH-Europe initiatives in research and education

### Improving knowledge on the efficacy of veterinary medicines

IFAH-Europe welcomes the Commission Communication of November 17<sup>th</sup> and specifically Action n° 10 which will introduce a **Target Pathogen Monitoring Programme** (TPMP) to fill gaps in our knowledge of the efficacy of veterinary products against the main target pathogens in livestock.

IFAH-Europe looks forward to this project being organised in collaboration with the national authorities of the Member States ensuring harmonised testing at the relevant laboratories in the Member States.

IFAH-Europe has already developed a draft protocol as it has been active in this area since 2000 via the CEESA/VetPath programme and would be happy to share its knowledge and experience with the authorities. We look forward to results being published on an annual basis.

Most bacterial strains are species-specific and so are unlikely to prosper within an individual of a non-host species. However, there is another route for the transmission of genes between bacteria of the same, or even different species, through the exchange of genetic material between bacteria.

**IFAH-Europe is investigating the potential risks of gene transfer between animal- and human-adapted strains of four bacterial species *Campylobacter*, *E coli*, *Salmonella* and *Enterococci*.** The project consists of a literature review and a risk assessment and is on-going.

Via this initiative, IFAH-Europe aims to provide the essential data needed to address questions on what contribution, if any, animal bacterial isolates make to the development of resistance in humans.

### Promoting the responsible use of medicines

IFAH-Europe was also one of the organisations responsible for setting up the **EPRUMA (European Platform for the Responsible Use of Medicines in Animals [www.epruma.eu](http://www.epruma.eu))** initiative in 2005. This is an alliance of organisations representing farmers, veterinarians, animal health companies, feed industry, a sustainable agriculture initiative, pharmacists and the diagnostics industry dedicated to promoting best practice in the use of veterinary medicines, including antimicrobial products. Its members recognise that the appropriate use of antimicrobials is only part of a spectrum of activities necessary to achieve high standards of livestock health and a safe food supply for the public. These products must be used in the context of bio-security, good housing, high quality nutrition, herd health plans and vaccination programmes along with good record keeping. The goal is to prevent animals from becoming ill (in line with the “prevention is better than cure” approach), and then if an antimicrobial treatment is needed, to ensure that each dose is used appropriately, in keeping with the guiding principle – ‘**As little as possible, as much as necessary**’.