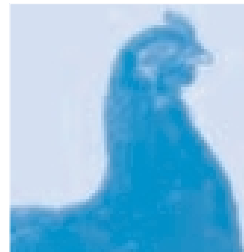


Guidelines

for the use of

quinolones

in veterinary medicine



Prudent therapeutic use of quinolones
in food-producing animals



Bayer's position:

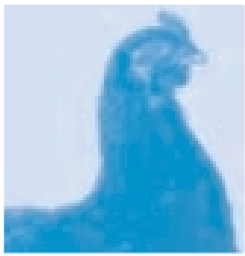
Expertise with responsibility

As one of the world's leading research-based chemical and pharmaceutical companies, Bayer's first concern is to ensure that its products offer the highest possible standards in terms of quality, efficacy and safety.

*With veterinary pharmaceutical products – as with any pharmaceutical product – this entails extensive efforts in research and development, utmost care throughout the production process and constant vigilance during marketing. In addition, prescribers and end users are expected to use the licensed products in a responsible way, according to the instructions provided by the regulatory agencies and Bayer. **Only in this way can maximum effectiveness with an optimal safety standard be achieved.***

The Bayer Group is one of the major partners of the health care profession. In the area of antimicrobials, the Group's long history of expertise has resulted in the development of two categories of quinolone-based products: Cipro®/Ciproxin®/Ciprobay® (active ingredient: ciprofloxacin) and Avelox®/Avalox® (active ingredient: moxifloxacin) for use in humans and Baytril® (active ingredient: enrofloxacin) for use in animals.

The use of antimicrobial agents such as quinolones can lead to the selection of resistant forms of bacteria. This is a naturally occurring biological phenomenon related to their application and is a feature common to all classes of antimicrobial agents. Generally, antimicrobial resistance is considered to be a major and complex problem which is of global concern. It is sometimes postulated that the use of antibiotics in veterinary medicine may compromise human health if resistant bacteria develop in animals and are transferred to people via the food



chain or the environment. **This is of particular concern for highly valuable classes of antibiotics such as the quinolones. The possible development of resistance to quinolones is constantly followed by the media with more than usual interest.** However, little evidence has been presented indicating that the use of quinolones in veterinary medicine has adversely affected quinolone therapy in humans. This has been confirmed in the report of a WHO Meeting in June 1998 entitled "Use of Quinolones in Food Animals and Potential Impact on Human Health". Experts attending the meeting recognized that quinolones should have a place in the therapeutic arsenal of the veterinarian. To safeguard the efficacy of quinolones in the future, the WHO Meeting and more recently additional groups of experts made a number of recommendations, primarily to develop strategies for prudent use and to establish susceptibility surveillance systems, the implementation and support of which Bayer began some years ago.

It is Bayer's policy to sustain the benefits of its products by promoting product stewardship as stipulated in the chemical industry's international "Responsible Care" program. Bayer is equally committed to protecting human health and to helping sick animals. **As the issue of resistance in people is of utmost importance and potential risks have not yet been fully quantified, Bayer has established a clear framework of precautions, extending the earlier "Bayer's guidelines" for responsible use of quinolones.** The principles, requirements and recommendations outlined in this brochure aim to ensure that the use of quinolone-based antimicrobial products for food-producing animals will provide maximum benefit to animal health and welfare without compromising human health.



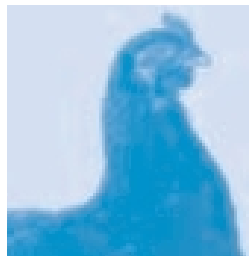
Quinolone use and emergence of resistance

It is Bayer's firm belief that there is a legitimate need in veterinary medicine for innovative agents such as fluoroquinolones. **Used properly, antimicrobials eliminate bacterial infections, hasten recovery of infected animals and improve animal welfare by alleviating pain, distress and lesions associated with disease.** They can also prevent the spread of infection from animal to animal, as well as from animal to man, by reducing the bacterial burden in infected animals.

While quinolones play an important role in the therapy of bacterial infections, their use – like the use of any other antimicrobial agent – must be expected to encounter resistance or some degree of reduced susceptibility at some time. Any discussion on the use of quinolones and the resistance issue must take into account the following:

- It is generally accepted that any treatment of infections with antimicrobials, including quinolones, may result in the emergence of resistant bacterial strains or strains with decreased susceptibility.
- There is a potential for pathogenic bacteria, including resistant strains, to be transferred from animals to humans through the food chain.
- Whether or not resistant bacterial strains originate from the use of antimicrobials in food-producing animals and significantly impair the efficacy of antibiotics in people, is the subject of ongoing scientific debate and requires further research.

There are a number of possibilities to limit the development of resistance. **They include research into the mechanisms of resistance and the search for new drugs, proper attention to preventive measures and commitment to prudent use.**



Antimicrobial research

Knowledge is one of the cornerstones in the fight against antibiotic resistance. Fundamental research into the mechanisms of resistance development is therefore one of the ways in which Bayer addresses the resistance issue. The understanding of bacterial flora epidemiology has to be advanced and the evolution and persistence of resistance as well as the mechanism of transmission of resistant bacteria from animals to people, are being investigated. Also, treatment regimens for quinolones (based on current pharmacodynamic principles) that would reduce the incidence of antimicrobial resistance have to be identified.

Concomitantly, Bayer is applying new technology in the search for more potent antimicrobial drugs as well as for new classes of antimicrobial drugs with novel modes of action. It is, however, very important to recognize that over the years it has become increasingly difficult to discover and to develop new classes of antimicrobial drugs. This underlines the necessity to take extensive measures to prolong the effective life of existing antimicrobials.

Alternatives to antimicrobials

Priority should therefore be given not only to drug research but, at the same time, to improving preventive veterinary medicine. For example, Bayer addresses this by its research into vaccine development and immune therapy. In addition, the company is developing a product which protects the natural intestinal flora from replacement by unwanted, potentially pathogenic bacteria including zoonotic enteropathogens such as Salmonella.



Extensive farm hygiene programs, together with optimal nutrition and husbandry, are basic requirements to limit the risk of disease outbreaks and, through this, the need to use antimicrobial drugs. Antimicrobials, including the highly valuable class of quinolones, should never be used as a substitute for good husbandry practices and should only be part of an integrated disease control program.

Prudent use

Prudent use of quinolones is important to reduce selection and dissemination of resistance and to ensure this class of antimicrobials remains effective. **Bayer, therefore, goes to great lengths to educate veterinary practitioners on the appropriate and prudent use of quinolones.** Together with its partners within the animal health industry, the company provides ongoing education for the veterinary profession and in 1998 introduced a code of practice on when and how quinolones should be prescribed and used. **Also, Bayer is monitoring bacterial resistance patterns in both human and animal populations.** These activities are primarily aimed at preventing the risk of resistance caused by inappropriate usage, as well as timely detection of any emerging resistance.

Bayer's principles, requirements and recommendations on the prudent use of quinolones are outlined on the following pages.

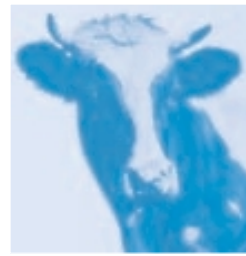


Guidelines on prudent use of quinolones

Principles

Bayer is committed to serving the animal health industry with state-of-the-art medication, i.e., products comprising high quality and efficacy standards. **At the same time, it is Bayer's declared policy that product safety and environmental compatibility have the same priority as quality and efficacy.** The following principles therefore govern Bayer's commitment to the use of quinolones:

- Quinolones are highly effective therapeutic drugs for both humans and animals and must be used in a responsible manner.
- Bayer strictly rejects any use of quinolones as performance enhancers. Bayer has never sought nor will it ever seek approval for such use.
- Bayer does not support the use of enrofloxacin in aquaculture.
- Bayer's quinolone products are not to be used routinely to prevent infection in healthy animals (prophylaxis). Bayer actively supports adherence to this principle.
- Concerns are being expressed about the illegal production and distribution of counterfeit quinolones. Bayer supports all legal measures to combat product piracy at a national and international level.
- To ensure environmental safety, Bayer conducts and endorses research on the degradability and bioavailability of quinolones in the environment.



Requirements

In order to ensure efficacious treatment and, at the same time, minimize possible risks of resistance selection, the following guidelines govern the use of quinolones in animal health:

○ **Quinolones are to be available only on veterinary prescription and should be used under the close supervision of a licensed veterinarian.** They are to be used for short-term therapy only. They should only be used in cases of serious infections, and never used for viral or trivial bacterial infections. Quinolone-based products, as they are prescription-only medicines, should be advertised only in veterinary professional journals or media, and not in the lay press. The marketing behavior of the manufacturers and distributors must support prudent use principles.

○ **Only fluoroquinolones approved for animal health are to be used.** These products are to be used only in strict accordance with the terms of their market authorization, e.g., only for the species, indications and dosages specified. Bayer, therefore, opposes extra-label use of quinolones in food animals. **It should be noted that all antimicrobials must undergo a very stringent regulatory review before they are approved for marketing.**

○ **Wherever possible, administration of quinolones is, in addition to an accurate clinical diagnosis, to be based on bacterial culture diagnosis and susceptibility testing of the causative pathogen(s)** to ensure that quinolones are the appropriate choice. In certain cases, however, it may be necessary to initiate therapy in the best interest of the patient, based on clinical diagnosis and experience of the veterinarian, before the results of susceptibility testing are available. To facilitate the performance of susceptibility tests, validated enrofloxacin discs and E-test strips specific for enrofloxacin are available.



○ If *Salmonella typhimurium* DT 104 (a serotype prone to develop decreased susceptibility to antimicrobials) has been historically reported or is detected in a herd or flock, treatment with a quinolone is not recommended. Instead, an eradication program should be initiated. In general, livestock and poultry producers should take steps to intensify *Salmonella* control measures in order to reduce the persistence or spread of *S. typhimurium* DT 104.

○ **It is of utmost importance that records are kept of antimicrobial usage.** Generally, infectious diseases should be documented and a record kept on the farm of the disease history, clinical diagnosis, bacteriological examination including susceptibility testing, antimicrobial treatment and therapeutic outcome. All relevant information for a given farm should be consolidated into a single database and available to the prescribing veterinarian. Routine periodic review of this information can be used to reassess the efficacy of quinolone treatment. Bacterial susceptibility testing on a regular basis, not only on the given farm but also of the local area or region, may help the practitioners to select the most appropriate and effective antimicrobial for their patients.

○ Special emphasis should be given to group therapy, previously designated metaphylaxis, i.e. short-term treatment at therapeutic levels of a group of animals, some of which have acute infections, others which are subclinically diseased and still others which are incubating disease. **Group therapy with a quinolone is only appropriate if all the above preceding requirements have been fulfilled.** Medications to treat a group of diseased animals can be added to the drinking water or the feed. In situations where it is essential to medicate a herd or a flock, this should encompass the smallest practical unit of animals. As for individual treatments, an oversupply should be avoided by selecting a package size as close as possible to the required amount of drug to be prescribed. Do not share or use leftover antimicrobials. Unused product should be discarded in an environmentally safe manner.



Recommendations

In addition to the above requirements, the following recommendations are designed to safeguard product safety and efficacy:

○ Bayer endorses professional education and information campaigns for veterinarians (including undergraduate and post-graduate level) and end users (all personnel involved in medication of animals) as well as for policy-makers and scientific journalists in order to ensure the rational use of quinolones. **Bayer veterinary staff must adhere to and promote the various guidelines and codes of practice concerning the use of therapeutic antibiotics in animals.**

○ **Co-ordinated and standardized bacterial susceptibility surveillance programs should be conducted over time to increase the knowledge of resistance trends in relevant bacteria.** These programs should be based on standardized laboratory techniques and on standardized veterinary break-points. Surveillance should target microorganisms of both veterinary and public health importance and samples should be collected at random from farms (pretreatment specimens), slaughterhouses and/or food of animal origin. A close collaboration with the authorities is required regarding the establishment of surveillance programs and analysis of results. Bayer veterinary staff should follow the programs and inform the veterinary practitioners of the outcome, enabling them to modify the drug therapy if necessary.

○ **Bayer supports the implementation of quality assurance programs such as HACCP (Hazard Analysis and Critical Control Point system) and other hygiene systems to reduce the level of bacterial contamination in animals and animal products.** Such public health safeguards minimize the pathogen load and thereby any significant transfer of antimicrobial-resistant pathogens to humans through the food



supply. Irrespective of the improvements made to reduce the levels of harmful bacteria in food, everyone needs to follow the established requirements for safe and careful handling of food, at home as well as in commercial kitchens.

○ **In addition to improved management and hygiene, alternative strategies aimed at reducing the need for antibiotics in disease control should be encouraged.** This includes disease eradication programs, vaccination, immunomodulation, competitive exclusion and, in the long-term, selecting farm animals for increased disease resistance.

○ Attempts should be continued to achieve pathogen-free breeder stocks. This will ultimately significantly diminish the overall use of antimicrobials. Bayer subsidiaries should explore ways to support pathogen eradication programs.

○ **Collaboration among the major stakeholders (drug manufacturers and suppliers, regulators, veterinarians and end users) as well as with international (e.g., OIE, WHO) and intergovernmental organizations is strongly encouraged.** Additionally, public health organizations as well as the food processing industry should be involved. This collaboration should focus on topics such as the development, distribution and implementation of guidelines for prudent use of antimicrobials, education programs and resistance surveillance. International cooperation and agreements are needed to curb emerging antibiotic resistance.

○ Research into the emergence and spread of antimicrobial resistance should be promoted. Also, it is essential to quantify the role of animals intended for food, as disseminators of antimicrobial resistant bacteria which can impact human health. This is necessary in order to define any risks to public health from the use of antimicrobials in food animals.



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International edition

Questions and Answers

What is antibiotic resistance?

Bacteria can be destroyed by so-called antibiotics - more accurately: antimicrobial drugs -, which are produced either by fermentation of microorganisms or synthetically. Antimicrobials are used to treat bacterial infections. Antimicrobial resistance is

the ability of certain bacteria, normally destroyed by antibiotics, to survive exposure to that antibiotic. Physicians and veterinarians prescribe antibiotics that are known to kill or inhibit growth of specific bacteria causing a particular disease.

How does antibiotic resistance occur?

Acquired antimicrobial resistance is a normal phenomenon which is an inherent consequence associated with any use of antimicrobial medication in any species. In contrast, natural resistance (intrinsic insensitivity to certain antimicrobials) is independent of selection pressure by antimicrobials. Acquired resistance is elicited by specific alterations within the bacterial cell such as a reduced cell wall or plasma membrane permeability, an altered target or by modifying enzymes. The major mode

of action of fluoroquinolones is to inhibit the bacterial enzymes DNA gyrase and topoisomerase IV which are essential for DNA replication in the cell. Antimicrobial resistance can be transferred from one bacterium to another by chromosomal mutation (resistance transfer to daughter organisms) or through exchange of genetic extrachromosomal material called plasmids (resistance transfer directly to other strains). It is assumed that resistance to quinolones is not plasmid-mediated under field conditions.

Why do animals need antibiotics?

Antimicrobial drugs are used to treat specific bacterial infections in a variety of companion and food-producing animals. In the case of livestock and poultry, antimicrobials are crucial for ensuring a safe food supply through healthier animals. Any reduction in the availability of classes of antimicrobials to veterinary medicine could result in increased animal suffering and death. When veterinarians have access to a variety of antimicrobials, they are better able

to select the most effective drug to treat specific infections and can alternate products to keep resistance at a low level. In all cases, animals should receive prompt and effective treatment as deemed necessary by the prescribing and supervising veterinarian.

Why use a quinolone to treat animals?

Medicines currently available have deficiencies in treating some important bacterial diseases of livestock and poultry such as respiratory and systemic infections (caused by e.g. *Pasteurella*, *E. coli*, *Actinobacillus*, *Mycoplasma*). Fluoroquinolones represent significant progress in the treatment of these diseases. Additionally, they

improve animal welfare by relieving suffering, shorter duration of the infection, and preventing death. Furthermore, they can assist in the provision of wholesome food for human consumption.

Widespread antibiotic use can lead to resistance. Are Bayer products contributing to a public health problem?

Bayer supports the use of fluoroquinolones in animals only when microbiological diagnosis and sensitivity testing and/or clinical experience shows them to be the drug of choice. They are available by prescription only and are to be administered under the supervision of licensed veterinarians. Moreover, the dosage and duration of therapy must comply with the label

recommendations to ensure adequate therapeutic levels, thereby minimizing risk of resistance development. When used in this manner, fluoroquinolones have a positive impact not only on animals but also on public health.

What is being done to ensure that the use of fluoroquinolones in animals will not have an impact on public health?

Prescription and distribution of quinolones is only recommended when strictly necessary. To minimize the risk, Bayer supports an extensive educational program for sales personnel and veterinarians, as well as livestock and poultry producers on the responsible use of antibacterial drugs. If the treatment is to be undertaken by an animal caretaker, the veterinarian and the animal owner should ensure that he/she has got written instructions on dosage and duration of treatment. Bayer

also monitors bacterial resistance patterns and encourages distribution systems that track the product to the end user. With such a distribution approach already implemented in the United States, Bayer maintains control of the product until sold to the veterinary practitioner. With this information Bayer can, and will, take appropriate steps to ensure that the use of the company's quinolone products is of benefit not only in the therapy of animals but also to public health.

How does Bayer ensure that poultry is dosed effectively?

When poultry are infected and have to be medicated (based on an appropriate diagnosis), it is necessary to treat the entire flock because bacteria are highly contagious and spread rapidly under flock conditions. Quinolone products have to be administered through an accurate dosing system under veterinary supervision that ensures therapeutic levels are achieved

to eradicate the bacteria. This therapy is administered for three to seven days. Once ample time has been allowed for the antimicrobial to leave the animal's body, processing for human consumption is allowed.

Which bacterial pathogens in animals can cause disease in man?

There are a number of bacteria in animals – so-called zoonotic bacteria – which can cause diseases in man. Well known examples are *Salmonella*, *Campylobacter* and some *E. coli* species. Zoonotic bacterial diseases have a global impact on human health, and their prevention and control are of great importance. Their route of trans-

mission is usually via the food chain but can also be by direct contact. With respect to quinolone resistance, the debate focuses mostly on *Salmonella typhimurium* DT 104 and on *Campylobacter jejuni*.

*What is the significance of salmonellosis in humans? What is meant by *Salmonella typhimurium* DT 104?*

Many strains of *Salmonella*, including *Salmonella typhimurium*, can be transmitted to humans, usually through the food supply, and may become a major cause of enteritis in man. Although the great majority of *Salmonella* infections in man result in self-limiting diarrheal disease, invasive infections may occur. Fluoroquinolones and cephalosporins are the drugs of choice for these infections which always require med-

ication. Much debate surrounds *S. typhimurium* phage type DT 104 which is currently the second most common *Salmonella* occurring in human beings. There is special concern for this phage type because it is often resistant to five classes of antimicrobials (ampicillin, chloramphenicol, streptomycin, sulfonamides, tetracyclines) and may develop decreased susceptibility to fluoroquinolones.

*What is Bayer's understanding of *Salmonella typhimurium* DT 104 and its link to quinolone susceptibility?*

Decreased *in vitro* susceptibility of DT 104 to quinolones has been noticed in some areas (e.g., England) but not in others (e.g., Ireland, Northern Ireland). As the minimum inhibitory concentration (MIC) values are elevated but remain clearly below the clinical breakpoints for resistance of quinolones used in human medicine, clinical efficacy is not expected to be affected. The prevalence of *Salmonella* serotypes fluctuates: in the UK the prevalence of DT 104 in humans declined since 1996/1997 and has now almost

reached the low level prior to the upsurge in the early 1990s. Recent (Scottish) findings suggest that DT 104 bacteria with reduced quinolone susceptibility may not have originated from livestock. Nevertheless, Bayer shares the concern and as a precautionary measure is making every effort to minimize potential risks. Vigilant susceptibility monitoring to detect and to manage resistance at an early stage is being conducted, in addition to the implementation of prudent use and education programs.

What is Campylobacter?

Campylobacter, predominantly *Campylobacter jejuni*, is one of the leading bacterial causes of foodborne illness in humans, causing diarrhea and abdominal pain which are usually mild and self-limiting. In severe cases, patients suffer from bloody diarrhea and fever lasting approximately one week. It is

rarely fatal. In contrast to the intestinal tract of humans, the intestine of poultry and livestock is colonized by *Campylobacter* strains without causing any disease symptoms.

Has Bayer seen a rise in Campylobacter colonisation in poultry or in resistant Campylobacter?

It is well known that colonization of *Campylobacter* usually occurs in poultry at an age of approximately 3 weeks. The degree of colonization varies from 0 to 100% depending on the hygiene status of the farm. Resistance of *Campylobacter* against several classes of antimicrobials, including quinolones, has been reported for strains obtained from both animals and man. This does not cause undue alarm because the high susceptibility of *Campylobacter* to macrolides remained unaffected. Besides quinolones, macrolides such as

erythromycin and azithromycin are the drugs of choice for the treatment of *Campylobacter* infection in humans. Moreover, alternative classes of drugs are available to treat campylobacteriosis. Irrespective of the choice of the antibiotic, the susceptibility of *Campylobacter* should be ascertained. The susceptibility to quinolones of other human bacterial pathogens remains unaffected.

*What is
E. coli
and what
significance has
E. coli 0157?*

E. coli, the abbreviation for Escherichia coli, is a predominantly aerobic bacterium found in the intestines of humans and animals. Some *E. coli* strains such as enterohemorrhagic *E. coli* (EHEC) can be a cause of bloody diarrhea and – in some severe cases – of kidney failure in humans. The most significant representative is *E. coli* 0157, which produces powerful toxins that can cause severe illness. Cattle are a common

source of these bacteria. Most illnesses are associated with consumption of undercooked ground meat and raw milk. *E. coli* infection can also be spread through person-to-person contact. Usually, infection disappears within a week without the need for antimicrobial medication. *E. coli* 0157 does not appear to be resistant to quinolones.

*Can anything
be done to reduce
the risk of
foodborne
bacterial illness?*

Yes. Since bacteria are naturally present in food, it is important to establish integrated hygiene management, including husbandry, food processing, storage and consumer handling. Thorough cooking will eliminate bacteria in food. Prompt refrigeration can prevent bacteria from contaminating leftovers,

and washing hands and utensils before and after handling raw meat and poultry can stop the spread of bacteria to other foods.

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