



April 6, 1999

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**Discussion Paper: "A Proposed Framework for Evaluating
and Assuring the Human Safety of the Microbial Effects of
Antimicrobial New Animal Drugs Intended for Use in
Food-Producing Animals"
Docket No. 98D-1146**

On behalf of our 7 million members and constituents, The HSUS offers the following comments on the Proposed Framework of The Food and Drug Administration (FDA).

We commend the FDA for taking this first step toward addressing the pending health crisis of antibiotic resistance. Implementation of a new drug approval process that takes into account antibiotic resistance prior to approval is an important step forward but is just a starting point. More must be done to restrict the routine use of antibiotics for growth promotion, particularly given the massive scale of such use in the face of ever-increasing loss of efficacy of drugs needed to treat disease in both humans and animals.

More than 40% of all antibiotics in the U.S. are used in agriculture with about 1/3 of all antibiotics in the U.S. used not to treat disease, but to promote growth in farm animals. That it is in the interest of public and animal health to cut back on this massive and unnecessary use of drugs should be obvious. But what has *become* obvious is that regulations will be required to bring this situation under control. Drug companies and representatives of the animal industry continue to refuse to provide important drug use information to the FDA and to make statements denying that there is any serious risk to consumers noting that no one in the U.S. has died from eating meat tainted with untreatable germs. We doubt the public would agree with this assessment. Most folks find it scary enough to learn of the increasing

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ineffectiveness of drugs previously relied on to treat disease and that between 1980 and 1996, the number of Salmonella infections that were highly resistant to antibiotics increased from 0.6% to 34%. And according to an article by Dr. Miller, in the *FDA Veterinarian* (July/August 1997): "A multi-drug resistant strain, *Salmonella typhimurium* DT104, has increasingly been associated with difficult to treat Salmonella infections in man and animals and increased deaths due to Salmonellosis in the United Kingdom."

We strongly support the FDA's move toward establishing a framework that will begin to bring this situation under control, and we urge the FDA to move forward with regulations that will truly protect animal and human health. The framework must also encompass existing uses of antimicrobials for food-producing animals as the greatest current risk comes from their overuse.

Antibiotics and Cheap and Plentiful Food

Both in the 'Statement of purpose' and in the "Introduction," the FDA makes the link between the use of drugs in farm animals and cheap food, such as the quote that follows: "FDA also recognizes that the use of antimicrobial drugs in food-producing animals is important in helping to promote animal health and helping to provide an abundant and affordable supply of meat, milk, and eggs." Yet according to the 1998 National Research Council study, a ban on subtherapeutic drug use in livestock would increase per capita costs a mere \$5 to \$10 per year. A small price for preserving the efficacy of drugs needed to treat disease. And promoting growth, not promoting animal health, is the reason for the use of approximately 80% of antibiotics used in agriculture (about 1/3 of all antibiotics used in the U.S.)

The statement connecting drug use with affordable food also does not take into account the myriad costs associated with the animal factories that rely on these drugs that are not reflected in the price paid at the supermarket. These expenses run the gamut from environmental pollution, worker and public health problems, and destruction of rural communities, to animal health and well-being costs. While not all of these are under the purview of the FDA, these 'costs' should nonetheless be mentioned in any discussion of how 'cheap' our food is.

Claims that the Framework will Result in Harm to Animal Health

It is indeed true that certain drug use promotes and protects animal health and well-being, but the majority of agricultural drug use is currently driven solely by economic motives and is not about promoting animal health. And given that we are facing a potential shortage of effective drugs to treat animal disease, it is disingenuous to suggest that it is in the best interest of animals or the public to simply move forward with approving more drugs without resolving the patterns of use and other problems that created the current crisis. It is also clear that having effective drugs available when needed to treat disease is threatened by the unnecessary and routine use of drugs in farm animals.

On-Farm Practices that Contribute to the Problem

Another area not receiving much serious discussion is the issue of how practices on animal factories contribute both to increased pathogen loads and impact the broader issues of animal health, antibiotic use, and antibiotic resistance.

Perhaps one of the best examples of a common practice that contributes to exacerbation of pathogen problems is that of the forced molting of laying hens, a practice of 'shocking' the hens' systems into higher productivity. The practice involves starving hens for up to two weeks, and in some cases, depriving them of water for days at a time. In addition to the intense suffering and mortality, this practice both makes birds more susceptible to salmonella infection and increases its transmission to eggs and other birds. The USDA's own research shows that forced molting makes hens far more susceptible to Salmonella and Peter Holt, Immunologist for the USDA's SE Poultry Research Lab stated, "While unmolted hens usually have to ingest about 50,000 Salmonella cells to become infected, molted hens need fewer than ten. Once infected, these hens shed far more germs in their feces than unmolted birds and are more likely to lay contaminated eggs." Yet despite both common sense and science backing the discontinuation of this practice on both food safety and animal health grounds, the industry continues the forced molting of laying hens for the production benefits.

Many examples can be put forth of known animal housing, handling, transportation and slaughter practices that cause unnecessary food safety risks, are known to increase pathogen loads, or result in the increased use of antibiotics. Many of the problems associated with these practices are documented by USDA's own data or that of industry experts, yet the practices continue.

The recent National Research Council report also raised a facet of this issue by looking at management practices that have implications for reducing the need for drug use including reducing overcrowding, improving hygiene, and switching to breeding strategies that focus on more than production traits. With science increasingly supporting what should be common sense, it is clear that crowding tens of thousands of genetically similar animals indoors in extremely close quarters is conducive to increased disease, drug use and the development of antibiotic resistance.

Prioritization of Regulatory Efforts by Category

For all the proposed categories, further clarification is needed regarding what categories currently available drugs would be placed in, as well as where new antimicrobials might be categorized. Regarding Category 1, these drugs are so critical to human health that they should be prohibited for any use in animal agriculture. Approval of the use of drugs such as fluoroquinolones in farm animals should be repealed, heeding the warnings of CDC prior to approval that such use could jeopardize the effectiveness of these drugs in treating human disease.

While establishment of categories for regulatory priorities would appear to be a sensible approach, our concern is that clean lines can not be drawn between drugs for human use versus those used only in animals.

The overuse of animal drugs and loss of drug efficacy has resulted in pulling important human drugs into animal agriculture. Fluoroquinolones provide an excellent example of endangering the effectiveness of an important class of human drugs to address the problem of drugs used in animal agriculture having lost their effectiveness. According to the Centers for Disease Control and Prevention (CDC), in 1990 there was no resistance to fluoroquinolones despite approval for humans in the late 1980's. Following approval for use in poultry in 1995, an alarming 18% rate of resistance is being reported for 1998.

Conversely, drugs that may not currently be important to human medicine may become important in the future, or the effectiveness of new human drugs may be jeopardized due to agricultural use of an antibiotic in the same class. Streptogramins illustrate this situation as a class of antibiotics where agricultural use of one antibiotic has already compromised the effectiveness of a newly developed antibiotic for human use from the same class. Synercid (a streptogramin) is a drug of last resort for the treatment of vancomycin-resistant infections in people. However, use of virginiamycin (another streptogramin) in farm animals appears to have caused the development of bacteria with resistance to other antibiotics in the same class, including Synercid.

Antibiotic use in animal agriculture may also select for multiple drug resistance that is then passed on to people. CDC's Dr. Angulo, asserts that animal and agricultural uses are responsible for the emergence of the most resistant strains of Salmonella, and that most antibiotic-resistant salmonellosis is acquired from food - especially foods of animal origin. Salmonella typhimurium DT-104 is resistant to 5 antibiotics and, according to CVM Director Steven Sundlof, raises concern about the potential establishment of a reservoir of drug-resistant organisms that can kill people and animals. As mentioned previously, the number of infections caused by this multi-drug-resistant strain has increased from 0.6% in 1980 to 34% in 1996.

Additionally, resistance genes can be transferred from antibiotic-resistant bacteria to other bacteria, thereby resulting in the transfer of resistance genes from harmless bacteria in animal products to pathogenic bacteria in people. And considering the environmental applications of antibiotics in orchards and aquaculture, spreading of animal manure on fields, and the recent discovery of VRE in chicken feed, it is becoming increasingly clear that the use of antibiotics and the development and transfer of resistance does not respect boundaries between animals, people, and the environment. Any comprehensive plan to address the pending health crisis of antibiotic resistance must limit all subtherapeutic and routine uses of antimicrobials.

Slaughter and On-Farm Resistance Monitoring Programs

Slaughterhouse data are, of course, of paramount importance to a successful monitoring program, and equally critical is that a sufficient number of samples are taken at slaughter.

We are in complete agreement with statements by the FDA that on-farm studies would be needed to collect information on resistance prevalence and associated risk factors to ensure target levels are not exceeded after approval. This is also necessary so that intervention and mitigation strategies could be investigated and initiated in a timely fashion. The challenge will be to develop a framework for on-farm monitoring that is practical yet effective.

An excellent point was also made by the CDC that on-farm studies could be useful to the industry in determining whether animal drugs or other on-farm practices are contributing factors in increased resistance. As addressed previously in our comments, current methods of raising animals for food raise myriad concerns for both animal and human health that must be addressed if the government is serious about getting unnecessary human health risks under control.

Whether referring to monitoring programs on-farm or at slaughter, more clarity is needed regarding who will be doing the testing, the numbers of samples that will be taken to yield results of significance, which animals will be tested, and specifically what they will be tested for. Clarification is also needed for exactly what will happen, and under what time frame, should resistance be found.

There also needs to be open sharing of all available data on drug use, resistance, pathogen loads, and related data. An excellent example is the need for sharing of FSIS slaughterhouse sampling data with the National Antibiotic Resistance Monitoring System.

It should also be recognized that environmental pollution by these resistant pathogens is another hazard that must be taken into consideration in a monitoring program. One key source of potential environmental transfer is the practice of spreading the manure from animal factories on fields, including crop fields. In fact, an Iowa State University study found that 100 of 120 soil samples collected from fields around Iowa where swine manure is applied contained tetracycline-resistant enterococcus.

Availability of Drug Sales and Use Information

In the face of the serious health crisis of increasing antibiotic resistance, it is unconscionable that there is not cooperation on the part of drug companies and the animal industry to provide adequate and transparent data on the use of drugs in farm animals - - particularly given the adamantness that decisions on this issue be science-based. It is clear that the FDA will need to require that this information be submitted to enable them to accurately chart the direct correlation between loss of susceptibility or increasing resistance trends with drug use. While requiring that detailed drug sales

information be reported as part of the “drug experience reports” is an excellent first step, the FDA must further strengthen the requirement for the reporting of drug use information.

Addressing the Problem of Antibiotic Resistance in Developed Nations

It is worth noting that the U.S. is far behind most developed nations in addressing this pending health crisis:

- Most developed nations have banned the subtherapeutic use of penicillin and tetracycline.
- The EU has banned the subtherapeutic use of key antibiotics, most recently including bans on bacitracin, spiramycin, virginiamycin, and tylosin. (Prior to the EU ban, Sweden, Finland, and Denmark already had specific bans in place.)
- The World Health Organization is calling for stopping the use of any antimicrobial agent for growth promotion if it is used in human therapeutics or known to select for cross-resistance to antimicrobials used in human medicine.
- Most developed nations don't allow environmental applications of antibiotics such as orchard applications or treating a body of water such as in aquaculture.

Unsuccessful attempts to address this problem in the U.S. go back to the 1970's. The FDA proposed restricting agricultural use of subtherapeutic antibiotics and began, but did not complete, proceedings to ban the subtherapeutic use of penicillin and tetracycline in animal feed. These attempts met with swift resistance from agribusiness interests. More recently, despite the FDA's extremely conservative approach to resolving this crisis, the CDC has taken a strong stance in support of the WHO position.

It is also worth pointing out that the swift opposition from animal industry interests in the past were not coupled with the industry putting any concrete framework in place to address the goals of limiting routine or subtherapeutic drug use in animal agriculture or related concerns for controlling the development of antibiotic resistance.

Need to Address OTC and Extra-Label Drug Uses

In light of the current situation with antibiotic resistance, the debate over the wisdom of allowing the widespread availability of over-the-counter drugs (including important antibiotics such as penicillin, tetracycline and gentamicin) for use in farm animals becomes even more critical. The OTC category severely limits the ability to get a true estimate of the magnitude of resistance and results in a huge gap in accountability for drug use. Reflecting these concerns in their global principles for prudent antibiotic use, The World Veterinary Association, International Federation of Agricultural Producers, and the Animal Health Industry (Comisa) included “professional supervision, particularly by veterinarians, and record-keeping [as] essential in the use and control of antibiotic products.” CDC's Dr. Fred Angulo also cited OTC drug use as an area in need of action, stating the need for FDA to reclassify the 13 antimicrobial agents approved for OTC use and place them under the purview of veterinarians.

The allowance of extra-label drug use must also be carefully restricted and monitored to enforce accountability and safety to animals and people alike. The HSUS recently filed a lawsuit against the FDA for opening yet another door for extra-label use by expanding this use to allow for "preventive" uses.

The FDA must include both categories of drug use in any comprehensive plan to address the prudent and safe use of drugs in animal agriculture and antibiotic resistance.

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