April 19, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Unapproved Animal Drugs; Docket No. FDA-2010-N-0528

The Center for Science in the Public Interest (CSPI)\(^1\) appreciates the opportunity to comment on FDA’s efforts to control the prevalence of animal drugs marketed in the United States without approval or other legal status. The overuse of antibiotics in food animals is a grave threat to public health, and we urge the agency to take immediate and decisive steps to ensure that drug residues—whether from approved, legal drugs or those used illegally—do not appear in food. Notably, FDA must concern itself not only with antibiotics, but also with a variety of other drugs being marketed for animal agriculture, including anti-inflammatory drugs, injectable vitamins, various topical solutions, shampoos, and antidotes. As the agency recognizes, many of these substances carry a potential human health risk and some are not approved for use in food animals.

FDA has requested comments specifically on its stated intention to limit its enforcement discretion for unapproved animal drugs. CSPI generally supports the intention to limit enforcement discretion on unapproved drugs, and urges the agency to look closely at its protocols around enforcement of approved drugs. Unapproved animal drugs—and the overuse of approved animal drugs—poses significant health risks for consumers, including drug residues found in meat, milk, and other animal products, and the evolution of antibiotic-resistant pathogens in food.

1. A Troubling Frequency of Drug Residue Violations in Dairy Cattle

CSPI has recently begun tracking drug residues in tissue samples from dairy cattle. The issues arising from that research are troubling, both from what they reveal substantively about threats to public health, and from what is missing from this important data set due to FDA’s inadequate milk sampling program.

\(^{1}\) CSPI is a non-profit consumer advocacy and education organization that focuses largely on food safety and nutrition issues. It is supported principally by the 900,000 subscribers to its Nutrition Action Healthletter and by foundation grants.
CSPI analyzed drug residues in dairy cattle tissue samples at slaughter over a one-year period from January 2010 to January 2011. Alarming, three drugs appearing on WHO’s critically important list appear in the samples (ampicillin, tetracycline, and oxytetracycline) and one illegal drug, gentamicin, appears in 6 percent of the tissue samples. Gentamicin can cause death of kidney cells and kidney failure, nerve damage, and vision and hearing loss. Notably, there is no tolerance for use in cattle because gentamicin is known to bind to kidney tissue for more than 18 months, meaning no withdrawal period is sufficient. E. coli has shown resistance to gentamicin.

From 793 samples, 27 percent were found to have residues of penicillin, an antibiotic categorized as “critically important” by the WHO. The potential human health impact of inadvertent penicillin exposure can include allergic reactions such as anaphylaxis, nerve damage, severe inflammation of the large intestine, swelling of the lips, tongue, or face, and bleeding.

Another 20 percent of samples contained residues of flunixin, a commonly used anti-inflammatory drug. Flunixin can cause fecal blood, gastrointestinal erosions and ulcers, and kinder necrosis in humans.

Seventeen percent of samples contained residues of sulfadimethoxine well-above the tolerance level allowed by USDA. Sulfadimethoxine has not been approved for use in humans, but side effects on animals can include toxic hepatopathy, vomiting, diarrhea, fever, hemolytic anemia, hematuria, and other severe symptoms.

CSPI has also compiled data related to the states with the largest number of residue violations across the U.S. from January 2010 to January 2011. In that period, California tissue samples at slaughter violated drug residue tolerances more than 200 times. Wisconsin dairy farms received 114 violations, and Pennsylvania farms incurred 69 violations. In total, one year’s worth of tissue samples revealed nearly 800 drug residue violations. Importantly, USDA data reveals that 67 percent of tissue residue violations were linked to adult dairy cattle, which account for only 7.7 percent of all slaughtered cattle. This points to an unanswered critical public health question: what drug residues are present in milk and milk products in the U.S.?

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2. Antibiotic-Resistance Related to Drug Use in Food Animals

Resistance is an inevitable consequence of antibiotic use; the more antibiotics are used, the more bacteria will develop resistance. Scientists have documented sophisticated biochemical mechanisms that allow bacteria to fend off or neutralize antibiotics and have shown the correlation with use of antibiotics in animals. Following the increasing use of antibiotics in animals for non-therapeutic purposes, resistance has begun to emerge more rapidly. This emerging resistance poses a major threat to the continued effectiveness of antibiotics used to treat human and veterinary illnesses. Further exacerbating the problem, fewer new antibiotics are being developed to replace those that are no longer effective.

Moreover, numerous studies have documented direct transference of antibiotic-resistant bacteria from animals to humans. After antibiotics were administered to animals to treat infections, the prevalence of antibiotic-resistant *E. coli* and *Campylobacter* bacteria also increased in humans. Other studies have confirmed that antibiotic-resistant *Campylobacter*, *Salmonella* Typhimurium DT 104, and *Salmonella* Newport have moved from animals to humans through foods of animal origin. Reflecting the fact that bacteria can develop resistance to numerous antibiotics at the same time, one group of related antibiotic-resistant *Salmonella* Newport strains is resistant to most available antimicrobial agents approved for the treatment of salmonellosis.

The human health consequences of these resistant organisms include more serious infections and increased frequency of treatment failures. Patients may experience prolonged duration of illness, increased frequency of bloodstream infections, increased hospitalization, and increased mortality. Health care costs increase with longer hospital stays and the need for more expensive antibiotics to fight resistant pathogens. The antibiotics used to treat resistant pathogens can be more toxic, with more serious side effects, to the patients.

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3. A Rise in Outbreaks of Antibiotic-Resistant (“ABR”) Pathogens

CSPI’s data on outbreak reporting indicates a rise in outbreaks due to antibiotic-resistant bacteria in each decade since the 1970s, with 40 percent of those documented outbreaks (14 out of 35) occurring in the last decade. Whether the increase is due to increasing use of antibiotics or to increased testing and reporting could not be determined. Outbreaks appear most commonly in dairy products (34 percent) and meat (37 percent), with nine out of 13 meat outbreaks occurring in ground beef. Of the available data set, which is presumed to be a severe underestimation of the actual occurrences of outbreaks linked to ABR pathogens, two outbreaks each were linked to poultry, pork, produce, and seafood, and one outbreak each was linked to eggs and multi-ingredient foods. The food vehicle was unknown in four of the outbreaks.

A total of 19,897 people were sickened from these 35 outbreaks, resulting in 3,061 hospitalizations and 26 deaths. The most frequently identified bacterial pathogen was Salmonella Typhimurium, which was implicated in 14 outbreaks causing 17,808 illnesses (40 percent of outbreaks) followed by Salmonella Newport, which was implicated in nine outbreaks with 586 illnesses (26 percent of outbreaks). Five other Salmonella subspecies were each implicated in one outbreak, with a total of 923 illnesses.

Of the 35 documented ABR outbreaks, 28 were linked to strains of antibiotic-resistant Salmonella. Twenty-four of these outbreaks had recognized antibiotic-resistance patterns. The responsible bacteria displayed resistance to a total of 14 different antibiotics and to at least one sulfonamide, which is a class of antibiotics. Of those antibiotics, six are classified by the World Health Organization (WHO) as “critically important” to human medicine and seven as “highly important” to human medicine.

CSPI has compiled a total of thirteen outbreaks related to meat products: nine in beef, two in poultry and two in pork. All of the beef-related outbreaks were associated with ground beef, with Salmonella Newport implicated in seven outbreaks and Salmonella Typhimurium implicated in two. Meat outbreaks were associated with 1,376 illnesses, 90 hospitalizations and 5 deaths.

Of the 12 outbreaks related to dairy products, seven were associated with milk and five with cheese products. In ten of the outbreaks, the vehicle was described as unpasteurized or raw milk and/or cheese made from unpasteurized milk. Pasteurized milk was responsible for two of the dairy-related outbreaks, including one exceptionally large one. All outbreaks related to dairy products were caused by Salmonella—nine by S. Typhimurium, two by S. Newport, and one by S. Dublin. Dairy-
related outbreaks sickened at least 17,122, hospitalized 2,860, and killed 19 people (including the huge outbreak caused by S. Typhimurium).

4. FDA Must Strengthen Its Milk Sampling and Enforcement Program

Currently, FDA’s milk sampling program is, by the agency’s own admission, woefully inadequate. Under the Pasteurized Milk Ordinance, FDA currently requires testing for only four of six specific drugs. Although these six listed drugs include penicillin and other commonly used beta-lactam drugs, the current list is incomplete and inadequate to protect public health. There are many other classes of drugs that may be in use on farms that are not routinely tested for in milk and milk products, and the human health risks related to their use may be severe.

CSPI urges FDA to increase its required sampling to test—at a minimum—for the drugs that have been found by USDA in its tissue sampling. The results of the testing program should be publicly available, and violators should face strict enforcement. FDA should increase inspections of dairy farms to ensure compliance with drug protocol, particularly in states with the highest number of violators, including California, Wisconsin, Pennsylvania, Minnesota, and New York. We recognize that the agency must include an assessment of the highest-risk producers in deciding where to target inspections, and suggest that the agency begin with those farms that have been identified as residue violators in meat products by USDA’s tissue sampling program.

Where drug residues are found, enforcement actions must be significant enough to serve as a deterrent. CSPI recommends that FDA impose significant fines for repeat violators, and shut down farms that are abusing drug protocols.

In addition, CSPI urges FDA to update its list of drugs important to human medicine to better reflect the thinking of the WHO. Currently, FDA’s 2003 list differs substantially from WHO’s 2009 list in its classification of drugs as “critically” or “highly” important. In fact, four drugs WHO classifies as “critically important” to human health are not classified at all by FDA: oxytetracycline, sulfadiazine, sulfa pyridine, and bacitracin. FDA should consider a program for periodic re-evaluation of this list to ensure that drugs important to human medicine—and the entire class of drugs from which they derive—maintain their efficacy.
5. Conclusion

CSPI appreciates the opportunity to assist FDA in strengthening its drug residue enforcement program. The use of drugs in animal production—whether to promote growth, prevent disease related to poor living conditions, or to treat legitimate illness—has a direct and profound impact on public health. FDA and its partner agencies must act decisively to protect the efficacy of drugs used for human health, and to create an atmosphere of responsible animal husbandry.

Sincerely,

Sarah Klein
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Center for Science in the Public Interest