KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
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August 27, 2010

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

Re: DRAFT GUIDANCE #209, THE JUDICIOUS USE OF MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS, Docket No. FDA-2010-D-0094

Introduction

Keep Antibiotics Working (KAW) appreciates this opportunity to submit comments on the Food and Drug Administration's (FDA) Draft Guidance # 209 on the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. Keep Antibiotics Working is a coalition of health, consumer, agricultural, environmental, humane and other advocacy groups with more than eleven million supporters dedicated to eliminating a major cause of antibiotic resistance: the inappropriate use of antibiotics in farm animals (www.KeepAntibioticsWorking.com).

DRAFT GUIDANCE #209 - NOTICE AND DISCUSSION DOCUMENT

The Notice. The availability of Draft Guidance #209, a discussion document announced in 75 Fed. Reg., 37450-51 on June 29, 2010, is found on the web at www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf.

According to the notice, Draft Guidance #209 is intended to inform the public of FDA's current thinking on the use of medically important antimicrobial drugs in food-producing animals in preparation for the development of strategies for reducing resistance.

The FDA's strategy would be aimed at reducing antimicrobial drug use in food animals by encouraging what the agency calls "judicious use of drugs," defined as the avoidance of "unnecessary or inappropriate use." The agency intends to issue additional guidance "in the near future" to provide more specific information on approaches for implementing the recommendations outlined in the draft guidance.

Draft Guidance #209. The first part of discussion document declares that "antimicrobial resistance and the resulting failure of antimicrobial therapies in humans is a mounting

public health problem of global significance" and summarizes the voluminous scientific literature and reports available on the issue.

The second part enunciates two recommended principles currently guiding the agency's thinking as it develops a strategy to respond to the problem. The principles are referred to as "recommendations" in the notice of availability of the guidance.

The first principle (Draft Guidance #209, p16) is that *" [t]he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health."* The guidance declares that the uses of drugs for production purposes are injudicious, while uses for treatment, control or prevention of diseases are necessary for assuring the health of food- producing animals. *id.* The guidance expands this position by noting that only "*some* prevention indications are necessary and judicious (emphasis added)." The guidance does not specify what those necessary preventive uses are but lists five factors that should go into the consideration of judiciousness of use: evidence of 1) effectiveness; 2) consistency with accepted veterinary practice; 3) a link to a specific etiologic agent; and 4) that the use is appropriately targeted; and 5) that no reasonable alternatives for intervention exist.

The second principle (Draft Guidance #209, p. 17) is that "*[t]he use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation."*

The agency asks for comments on how the FDA can best "use its regulatory authority and take non-regulatory measures to support the two principles."

General Comments

KAW agrees with the FDA that the overuse of antibiotics in food animals has created a serious global public health problem for both human and animals. We are pleased that the FDA intends to develop a strategy to address this problem and that it plans to issue guidance implementing that strategy in the near future. This problem has gone unaddressed for far too long.

While we do not necessarily disagree with the principles as stated, we are dismayed by the strategy that the discussion document appears to embrace. As far as we can deduce from the discussion of the two principles, the agency is headed toward a two-part strategy that would attempt to persuade the drug industry to voluntarily withdraw label indications for production uses of antibiotics, such as growth promotion, and then attempt to subject therapeutic and preventive uses of the drugs to greater veterinary oversight.

In our view, as laid out below in greater detail, such a strategy will not lead to substantial reductions in antibiotic use in animals and thus will not seriously address the tidal wave of costly, resistant human and animal disease we now confront.

To seriously address the overuse of drugs in animal agriculture, FDA should use its regulatory authority to **cancel** injudicious label indications for routine disease prevention and control uses, as well as production uses.

KAW agrees that the agency should put antibiotic uses under greater veterinary control by requiring prescriptions or veterinary feed directive orders for all medically important antibiotics, but strongly believes that it cannot rely on veterinary oversight as the sole measure to reduce inappropriate preventive and therapeutic use.

Whatever strategy the agency adopts, the next guidance or regulation issued by the FDA on this public health threat should explain specifically how the strategy will reduce antibiotic use and establish a time line for accomplishing those steps.

Draft Guidance #209 correctly recognizes that the use of antimicrobials in food-producing animals creates a risk to public health through the selection of resistant bacteria. However, it fails to describe any concrete actions that the FDA plans on taking to manage this risk. Instead, Draft Guidance #209 lays out two additional judicious use principles to be added to already existing guidelines adopted by livestock industry trade associations, without indicating how the FDA intends to ensure that these principles are followed. There is no evidence that the judicious use guidelines so far adopted have had any impact on how antibiotics are used in food-producing animals or, more importantly, on antimicrobial resistance.

By addressing reductions in antibiotic use through new judicious use principles in a guidance document instead of a rule making, the FDA indicates that it is seeking voluntary changes instead of binding regulatory change. Given the financial interests of antimicrobial users, antimicrobial manufacturers, and others such as veterinarians and feed manufacturers that profit from the sale of these products, it is unlikely that voluntary efforts will lead to significant reductions in use. The time and effort spent on cajoling the industry to follow principles with which they do not agree would be better spent laying the groundwork for taking the necessary legal steps required for the FDA to fulfill its mission of protecting public health.

KAW asks that FDA release a specific plan of action describing which uses in particular it believes are unsafe or unnecessary, along with a description of what steps the agency will take to end the inappropriate use of such antibiotics in food-producing animals. This plan should include a timeline in order to ensure accountability. Given that Guidance #152 is the preferred method by the FDA for assessing the safety of antimicrobial drugs in food-producing animals, KAW recommends that this new plan include risk assessment of drugs using Guidance #152. KAW also recommends the withdrawal of the uses of drugs found to be at high risk that are incompatible with the risk management options in Guidance #152.

Draft Guidance #209 fails to provide a clear plan of action, which should include an enforcement mechanism and timetable, for reducing the inappropriate use of antibiotics in food-producing animals. Draft Guidance #209 also mischaracterizes how

antimicrobials are used for disease prevention in food-producing animals and subsequently underestimates the public health risk of these types of uses. While some preventive uses are limited to targeted groups of animals, the bulk of the antimicrobials used for disease prevention or control in food-producing animals are administered to entire herds or flocks for problems such as necrotic enteritis control in poultry and liver abscess control in cattle. Some antimicrobials - such as ceftiofur used in poultry hatcheries for control of *Escherichia coli* infections - may be administered not only to whole flocks but to whole segments of the livestock industry. As Draft Guidance #209 (p. 14) states, giving antimicrobials to whole herds or flocks, as is often done with antibiotics for disease control or prevention, creates a qualitatively higher risk of resistance than from treating an individual animal.

The FDA's role in determining how antimicrobials are used on farm is limited to assuring that they are safe and effective. On what basis does the FDA believe that the risk of feeding low-level doses of a particular antibiotic to food-producing animals for routine disease prevention is any safer than doing so for growth promotion? If a drug used for disease control creates the same or higher risk than a drug used for growth promotion, then FDA policy should reflect that. For example, it is unclear how the FDA can argue that feeding cattle bacitracin for growth promotion, a drug of low importance for human medicine, creates a greater public health risk than feeding cattle tylosin, a critically important drug, for liver abscess prevention. KAW recommends that the FDA's principles be amended so that antimicrobials only can be used for prevention when there has been a diagnosis of illness in the group of animals to be treated.

Draft Guidance #209 attempts to address the problem of inappropriate preventative use by stating that antimicrobials should only be used under veterinary supervision. While KAW supports greater veterinary oversight of antimicrobial use, there is little evidence that this would have a significant impact on the overuse of antimicrobials in food animals. Veterinarians hired by industrial animal agriculture operations are under pressure to satisfy their clients, just as doctors are under pressure from their patients to write antibiotic prescriptions that may be unwarranted. Veterinarians also will have a direct conflict of interest if they profit from the sale of antibiotics. It is unrealistic to expect veterinarians to provide a meaningful check on indiscriminate preventive uses, especially in the absence of specific rules from the FDA.

Draft Guidance #209 (p. 16) lays out five factors to consider when determining whether a specific preventative use is appropriate, but FDA has no authority to ensure that veterinarians consider these factors. The FDA could review the available data on existing approvals for disease prevention and determine which approvals are appropriate, but Draft Guidance #209 gives no indication that FDA intends to take this step. Because of the ready availability of inexpensive antimicrobials, and the likelihood that veterinarians in the employ of producers will accommodate their wishes, producers will have no incentive to put in place alternative practices that have even slightly higher costs, such as modified diets.

Specific comments

Page 4. Paragraph 1. Draft Guidance #209 inaccurately suggests that the terms "nontherapeutic" or "subtherapeutic" use are synonymous with production use. FDA traditionally has considered any drug used at a concentration of under 200 g/ton for over two weeks to be "subtherapeutic," independent of whether it is used for production or disease prevention (WHO, 2003). The term "subtherapeutic" still appears in the Code of Federal Regulations and clearly includes antibiotics used for disease prevention (21 CFR 558.15). Subtherapeutic is also used in this way in the published literature. See for example McBride (2010), Cox et al. (2003), and DuPont and Steele (1987). Similarly, the term "nontherapeutic" as used in the published literature and in legislation pending in Congress refers to antibiotics used for purposes other than disease treatment, including both growth promotion and routine disease prevention.

Page 14. First full paragraph. Draft Guidance #209 suggests that antibiotics used to prevent or control disease are not administered to whole flocks or herds of animals. As KAW noted above, this is inaccurate as drugs are routinely administered to whole herds or flocks for disease prevention. This is important because the reason for use of an antibiotic does not change the risk of resistance. It is the extent of use that changes the risk, and the extent of use is often indistinguishable between growth promotion and disease prevention purposes.

Page 14. 3rd full paragraph. Draft Guidance #209 states that there are "practical" differences between applying Guidance #152 to the pre-approval process of new drugs and to the safety review of currently approved drugs. The FDA states one such difference is that Guidance #152 guides upstream product development, but the impact Guidance #152 has on upstream product development by drug sponsors does not have any bearing on whether or not it is suitable for use by the FDA in determining whether a drug is safe. Sponsors use Guidance #152 to guide product development precisely because FDA has determined that it is the appropriate tool to determine safety.

Draft Guidance #209 then states, "FDA may examine certain currently-approved products to determine whether such products appear consistent with GFI #152," but says this is different than determining whether a drug is unsafe. This approach by the FDA in Draft Guidance #209 undermines Guidance #152 as a risk assessment tool. Either it is an appropriate tool for determining whether or not a proposed or existing "use" is safe or it is not. The FDA seems to suggest that risk assessment under Guidance #152 can only result in a finding of safety and that if a drug is found unsafe under Guidance #152, still further evidence must be found to show that it really is unsafe.

Page 14. Final paragraph. FDA believes voluntary actions by drug manufacturers can be an effective way to address concerns. The aim of the current policy is to improve human health through reducing the use of medically important antimicrobials in food-producing animals by reducing production uses and uses without veterinary oversight. It is against the short-term financial interest of antimicrobial manufacturers and thus highly unlikely that they will voluntarily take steps to reduce antimicrobial use in food-producing animals and thus reduce their sales. FDA is clearly concerned about the legal challenges

of initiating a non-voluntary withdrawal, but there is no reason to believe that the barriers to voluntary actions are any lower. Time spent negotiating with drug sponsors could easily take as long as legal action, with the outcome equally uncertain. Given the financial perspective of the companies, the final outcome of the voluntary approach may likely be cosmetic and not substantial.

Page 15. Full paragraph 2. FDA states that Guidance 152 has been effective but notes that it intends to update the drug importance ranking. KAW supports reevaluating the medical importance of drugs under Guidance #152, particularly with respect to drugs used to treat pathogens like methicillin-resistant *Staphylococcus Aureus* (MRSA), which have only recently been identified as having a livestock source. In addition to updating the list, FDA should also re-examine the criteria which currently downplay the importance of drugs used for treating extra-intestinal infection of gut organisms such as *Escherichia coli* and *Enterococcus spp.* even though extra-intestinal infections by these organisms are more likely to require antimicrobial treatment than gastroenteritis. KAW also recommends that Guidance #152 be updated to include other ways that resistance may spread – occupational and environmental pathways– in addition to the food-borne pathway.

Page 16. Principle and bottom two paragraphs. This entire section contains contradictory language related to the use of antimicrobials for disease prevention. At some points, Draft Guidance #209 describes all uses other than for production purposes as necessary, but later qualifies this by stating that antimicrobials when used for prevention are only appropriate when five factors are considered before they are used. KAW recommends that the principle be modified to include more information about what uses actually are appropriate.

Suggested language:

> Principle: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health. It is not considered necessary for assuring animal health to use antimicrobials for production purposes or for disease prevention when there is no identified etiologic agent or when reasonable alternatives for prevention – including better animal husbandry practices – or intervention are available.*

Conclusion

The FDA needs to look at how antimicrobials are used for disease prevention in food animals and stop ignoring the evidence that they are often used in exactly the same manner as for growth promotion, thus creating the same public health risks. Clearly some prevention uses are legitimate, but the widespread routine use of antimicrobials in whole herds or flocks - or even whole segments of the livestock production industry - creates significant public health risk that the FDA must address.

KAW asks that the FDA stop further delays and make public what meaningful steps it intends to take to address the problem of the inappropriate use of antimicrobials in food-producing animals, including the use of antimicrobials for routine disease prevention.

This plan should indicate what antimicrobial uses FDA believes are inappropriate, along with a timeline of steps the FDA intends to take to ensure that antimicrobials are used appropriately. While it is commendable that FDA is attempting to minimize the impact of change on livestock producers, FDA cannot let the effort to protect livestock producers' short-term interests interfere with FDA's mission to protect public health. Delay has consequences, as people become ill with more difficult to treat diseases and bacterial populations adapt, potentially reducing the effectiveness of future steps to reduce antimicrobial use. This topic has been discussed for more than 30 years. It is now time for the FDA to take concrete steps to protect public health.

Sincerely,

Richard R. Wood
Steering Committee Chair
Keep Antibiotics Working

And the following organizations:

Michael F. Jacobson, Ph.D.
Center for Science in the Public Interest

Steven Roach
Food Animal Concerns Trust

Michael Greger, M.D.
Humane Society of the United States

David Wallinga, M.D., M.P.A.
Institute for Agriculture and Trade Policy

Nancy Donley
Safe Tables Our Priority

Margaret Mellon, Ph.D., J.D.
Union of Concerned Scientists

Hannah Connor, J.D.
Waterkeeper Alliance

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