Comments of Consumers Union on
Food and Drug Administration (FDA) Draft Guidance: the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals
Docket No. FDA-2010-D-0094
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Consumers Union[1] (CU) welcomes the opportunity to comment on FDA's Draft Guidance #209 on the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. We completely agree with the FDA that the overuse of antibiotics in food animals has created a serious global public health problem for both human and animals and think the Guidance does a very good job of summarizing the key scientific reports on this topic. We commend FDA for addressing this problem by developing a policy framework regarding the judicious use of medically important antimicrobial drugs in food-producing animals. We also strongly agree with FDA that injudicious use of antimicrobial drugs should be minimized and eliminated, where possible, in order help minimize antimicrobial resistance development. In general, we do support the two principles laid out by the FDA in Draft Guidance #209: 1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and 2) limiting such drugs to used in food-producing animals that include veterinary oversight or consultation. However, we have some concerns regarding these principles and regarding FDA's approach to this problem.

Consumers Union has been advocating for the curtailment of antimicrobial use for sub-therapeutic purpose in food animal production for more than thirty-five years. During that time, the problem of harmful bacteria becoming more resistant to antimicrobials has only grown. Thus, it is our opinion that FDA's definition of "injudicious use" is too narrow and needs to be expanded to include *all* sub-therapeutic uses of medically important antimicrobial drugs, including use for "routine prevention of disease." The definition should not simply be restricted to "production" (e.g. increasing rate of weight gain or improving feed efficiency). In addition, since the Guidance is voluntary, we do not think it will be effective enough in reducing injudicious use of antimicrobials. Consequently, we believe that FDA should ban the subtherapeutic use of medically important antimicrobials. In addition, to help minimize antimicrobial resistance development, we think that FDA should require reporting and disclosure on the sales and use of all antimicrobials used in animal agriculture in order to properly track the magnitude of the problem.

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[1] *Consumers Union, publisher of Consumer Reports, is an expert, independent nonprofit organization whose mission is to work for a fair, just, and safe marketplace for all consumers and to empower consumers to protect themselves. To achieve this mission, we test, inform, and protect. To maintain our independence and impartiality, Consumers Union accepts no outside advertising, no free test samples, and has no agenda other than the interests of consumers. Consumers Union supports itself through the sale of our information products and services, individual contributions, and a few noncommercial grants. Over 7 million people subscribe to Consumer Report or Consumer Reports online.*

Specific comments on the Guidance and the two proposed principles follow.

Production use of antimicrobials is not synonomous with "nontherapeutic" or "subtherapeutic"

In the Introduction, FDA states that the Guidance "addresses the use of medically important antimicrobial drugs in food-producing animals for production or growth-enhancing. These uses, referred to as production uses in this document, are often also referred to as 'nontherapeutic' or 'subtherapeutic' uses."[2]

We disagree with FDA that "nontherapeutic" and "subtherapeutic" uses are synonymous with "production uses." The Code of Federal Regulations clearly defines subtherapeutic use to include disease prevention. For example, the section entitled "Antibiotic, nitrofuran, and sulfonamide drugs in the feed of animals", refers to "currently approved subtherapeutic (increased rate of gain, **disease prevention**, etc.) uses in animal feed of antibiotics"[3] emphasis added. In addition, as noted in the 1988 Institute of Medicine report, *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed*, "The Center for Veterinary Medicine considers any extended use of antibiotics in feed at 200 g/ton or less beyond 2 weeks as 'subtherapeutic use,' whether it is for growth enhancement **or disease prevention**. . . Levels approved for growth claims and disease prophylaxis are usually lower than those approved for disease treatment"[4] emphasis added. Thus, FDA has traditionally defined subtherapeutic use as including both growth promotion and disease prevention.

In addition, "subtherapeutic use" is also defined this way throughout the scientific literature. A 2008 paper on subtherapeutic use of antimicrobials in hog production states, "Antimicrobial drugs are fed to hogs at sub-therapeutic levels **to prevent disease** and promote growth."[5] A 2003 paper on subtherapeutic levels of antimicrobial in turkeys stated, "Since the 1950s, antimicrobials have been added to poultry feed at sub-therapeutic levels **to minimize illness** and promote growth"[6] emphasis added. A 2005 paper on subtherapeutic use of antimicrobials in beef cattle states, "In North America, antimicrobial agents have been used in feed for ca. 50 years for the prevention of disease and as growth promoters in beef cattle. . . . The subtherapeutic application of antimicrobial agents to cattle may contribute to the emergence of resistant pathogenic bacteria, and the continuous administration of antimicrobials at relatively low

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[2] Pg. 4 in *Draft Guidance* #209
[3] 21 CFR §558.15(a)
[4] Pg. iii in Institute of Medicine (IOM). 1988. *Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed*. National Academies Press. Washington, D.C.
[5] Pg. 270 in McBride, WD, N Key and K Matthews. 2008. Subtherapeutic antibiotics and productivity in U.S. hog production. *Rev. Agr.*, 30(2): 270-288.
[6] Pg. 32 in Cox, NA, Craven, SE, Musgrove, MT, Berrang, ME and NJ Stern. 2003. Effect of sub-therapeutic levels of antimicrobials in feed on the intestinal carriage of *Campylobacter* and *Salmonella* in turkeys. *J. Appl. Poultry Res.*, 12: 32-36. At: http://japr.fass.org/cgi/reprint/12/1/32.pdf

concentrations has been hypothesized to increase the likelihood of resistance development."[7]

It is extremely important to define subtherapeutic use properly because the quantity of antimicrobials for routine disease prevention is significantly larger than the quantity used for growth promotion. The way to minimize the threat of antimicrobial resistance is to minimize the use of antibiotics, basically only using them for therapeutic purposes, and not using them for subtherapeutic purposes. According to the 1988 IOM report cited above, in 1985, some 8.316 million kilograms of antimicrobials were used in livestock (e.g. cattle, swine and poultry) in the US.[8] Of that quantity, 64% (or 5.258 million kg) was used for disease prevention, 24% (2.046 million kg) for growth promotion and 12% (1.012 million kg) for therapeutic use. Thus, 88% of all microbial use consisted of subtherapeutic uses. Also, according to the IOM report, 63% (5.219 million kg) of all the antimicrobials were used in swine production.[9] Within swine production, 68.5% (3.578 million kg) of the antimicrobials were used for disease prevention, 26.5% (1.391 million kg) for growth promotion and only 5% (250,000 kg) for disease treatment. Thus, 95% of all antimicrobials used in swine production are for subtherapeutic uses. These data clearly show that the bulk of the antibiotic use is for disease prevention, followed by growth promotion. As a result, both uses must be targeted if we are to deal with the problem of injudicious use of antimicrobials.

A 2001 report published by the Union of Concerned Scientist (UCS), *Hoggin It: Estimates of Antimicrobial Abuse in Livestock*, attempted to update the 1985 data used for the 1988 IOM report by producing a transparent estimate of the quantities of subtherapeutic use of antimicrobials in swine, poultry and cattle in the late 1990s. Overall, UCS estimated that the total nontherapeutic (or subtherapeutic) use of antimicrobials in swine, poultry and cattle amounted to 24.6 million pounds[10], which is about one-third higher than the IOM estimate of 8.316 million kg (or 18.3 million pounds). In addition, they estimate that 70% of the antimicrobials used in swine, poultry and cattle are used subtherapeutically. Thus, the UCS estimate is lower than the IOM; UCS estimates that 70% of all antimicrobials are used subtherapeutically, compared to IOM's estimate of 88%. Either way, subtherapeutic use of antimicrobials does constitute a huge use of antimicrobials in animal agriculture, and the problem still persists, given the overall increase in amount of antimicrobials used subtherapeutically in animal agriculture.

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[7] Pp. 3872-3873 in Inglis, GD, McAlister, TA, Busz, HW, Yanke, LJ, Morck, DW, Olson, ME and RR Read. 2005. Effects of subtherapeutic administration of antimicrobial agents to beef cattle on the prevalence of antimicrobial resistance in *Campylobacter jejuni* and *Campylobacter hyointestinalis*. *Applied and Environmental Microbiology*, 71(7): 3872-3881

[8] Table IV-9, pg. 75 in IOM op cit.

[9] Id

[10] Mellon, M, Benbrook and KL Benbrook. 2001. *Hogging It: Estimates of Antimicrobial Abuse in Livestock*. Union of Concerned Scientists, Washington, D.C. At: http://www.ucsusa.org/food_and_agriculture/science_and_impacts/impacts_industrial_agriculture/hogging-it-estimates-of.html

For the swine industry, 2004 data noted in the McBride study cited above clearly show that more antibiotics are more widely used for disease prevention than for growth promotion purposes.[11] In addition, some antimicrobials—such as ceftiofur, used in poultry hatcheries for the control of *E. coli* infections, or tylosin, used for liver abcess control in cattle—may be administered to whole flocks or herds.

FDA then incorrectly implies that use of antimicrobials for disease prevention purposes does not entail treating entire flocks or herds of animals, which supposedly only occurs with production purposes: "administration of medically important antimicrobial drugs to entire herds or flocks of food-producing animals (e.g. for production purposes) would represent a use that poses a qualitatively higher risk to public health than the administration of drugs to individual animals or targeted groups of animals (e.g. to prevent, control, or treat specific diseases)."[12] While we absolutely agree that treating entire herds or flocks with antimicrobials does pose a higher risk to public health than treating individual or small groups of animals, we note that the subtherapeutic use of antimicrobials for disease prevention does indeed include treating entire herds or flocks, as the examples of ceftiofur in poultry hatcheries or tylosin in cattle demonstrate. In addition, subtherapeutic use of antimicrobials for disease prevention represents the major use of antimicrobials in animal agriculture and therefore must be addressed.

In the Introduction, FDA notes that their Guidance for Industry (GFI) #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern," is "premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs."[13] We agree completely. Reducing the risk of generating antimicrobial resistance means reducing the amount of antimicrobials used. This means concentrating on subtherapeutic uses of antimicrobials—which constituted 88% of all antimicrobials used in animal agriculture in 1985,[14] or 70% in the late 1990s.[15] In addition, since the subtherapeutic use of antimicrobials for disease prevention purposes constitutes the bulk of antimicrobials (64%) used in livestock agriculture according to IOM,[16] FDA must also look at ways to stop this use as well as the use for growth promotion purposes, which constitutes only 24% of all antimicrobials used.[17]

First Principle: ***The use of medically important antimicrobial drugs for food-producing animals should be limited to those uses that are considered necessary for assuring animal health.***

While we agree with this principle, we disagree with FDA about what constitutes "necessary" use. We agree with FDA that uses of antimicrobials for production purposes

[11] Pg. 273 In McBride et al. 2008. *Op cit.*
[12] Pg. 14, *Draft Guidance* #209
[13] Id
[14] IOM, *Op cit.*
[15] Mellon et al. *Op cit.*
[16] IOM, *Op cit.*
[17] IOM, *Op cit.*

(e.g. growth promotion or feed efficiency) do represent an injudicious use of antimicrobials that should be curtailed. However, we disagree with FDA that subtherapeutic use of antimicrobials for disease prevention purposes is a necessary use for assuring animal health, as discussed above.

It is our opinion that FDA appears to be taking contradictory positions on this issue. First, FDA states that use of antimicrobials for disease prevention is necessary: "FDA considers uses that are associated with the treatment, control, or **prevention of specific diseases** . . . to be uses that are necessary for assuring the health of food producing animals"[18] emphasis added. Yet, in the next paragraph, FDA seems to recognize that some uses of antimicrobials for disease prevention purposes may constitute an injudicious use of antimicrobials, noting: "FDA believes that *some prevention indications* are necessary and judicious"[19] emphasis added. This implies that *other* prevention indications are neither necessary nor judicious. FDA then goes on to list five "factors to consider when determining the appropriateness of a preventative use . . . (1) evidence of effectiveness, (2) evidence that such a preventative use is consistent with accepted veterinary practice, (3) evidence that the use is linked to a specific etiologic agent, (4) evidence that the use is appropriately targeted, and (5) evidence that no reasonable alternatives for intervention exist."[20] While this list may be helpful, FDA currently has no regulatory authority to require that these five factors be considered before using antimicrobials subtherapeutically for disease prevention purposes. Thus, FDA has created a large loophole in their proposed policy (e.g. Draft Guidance #209) by allowing subtherapeutic use of antimicrobials for disease prevention purposes. Again, this approach is less preferential to an *absolute* ban, both in terms of implementation and enforcement.

We urge FDA to make a distinction between antimicrobial uses for treatment, control or prevention. Antimicrobials used to treat or control disease are used at therapeutic levels (e.g. over 200 g/ton), while the vast bulk used for prevention are applied at subtherapeutic levels. Thus, FDA should consider use of antimicrobials for treatment or control purposes to constitute judicious use, while use for prevention purposes should constitute an injudicious use. It is important to keep in mind that the goal of this Principle and FDA policy in this area is to minimize the development of antimicrobial resistance. The way to minimize antimicrobial resistance is to minimize antimicrobial resistance selection pressure, accomplished by reducing the use of medically important antimicrobial drugs. Since subtherapeutic use of antimicrobials for disease prevention account for 64% of all antimicrobials used, while subtherapeutic use for production purposes accounts for only 24%, it is clear that in order to dramatically reduce the use of medically important antimicrobial drugs, one must tackle their subtherapeutic use for disease prevention.

FDA could dramatically reduce antimicrobial selection pressure by banning all subtherapeutic uses of antimicrobials, which, in 1985, represented 88% of all

[18] Pg. 16, *Draft Guidance* #209, *Op cit.*
[19] Id
[20] Id

antimicrobial use[21], and an estimated 70% in the late 1990s.[22] We therefore urge FDA to declare that subtherapeutic use of antimicrobials for disease prevention purposes is injudicious.

Should the FDA decide not to declare all subtherapeutic uses of antimicrobials for disease prevention as injudicious, then FDA should take rigorous steps to allow only limited use of antimicrobials for disease prevention purposes, and not allow this to become a loophole that results in large amounts of antimicrobials continuing to be used. The five factors that FDA proposes to use in deciding if a disease prevention use of antimicrobial is judicious are not sufficiently rigorous enough on their own to guarantee that antimicrobial use for such purposes would be reduced. Consequently, if FDA decides that some subtherapeutic uses of antimicrobials for disease prevention are necessary and thus constitute judicious use, we urge FDA to also set a target goal of reducing subtherapeutic use of antimicrobials for disease prevention by a specific amount (for example 75%) and require a timetable for such a reduction. In order to monitor and enforce such a provision, FDA should require reports of the quantities of antimicrobials used for each type of purpose: treatment or control, disease prevention, and growth promotion purposes. FDA should ask for new authority to require such reporting if no such authority is currently available. We strongly urge FDA that if the goal is to eliminate subtherapeutic use of antimicrobials for production purposes, and should have a timetable for such an elimination.

Second Principle: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight and consultation.*

We strongly support this principle and believe that all antimicrobials used in animal agriculture should only be used under veterinary supervision. However, even if all antimicrobials were used under veterinary supervision, we do not believe this would lead to a significant reduction in the overuse of antimicrobials in food animals. Veterinarians hired by industrial animal agriculture operations are under pressure to satisfy their clients. Large numbers of animals kept in close proximity in industrial animal agriculture operations increases stress on the animals and decreases their immune systems. In addition, such tight quarters mean that if any animal gets sick, a disease can quickly spread to all other animals. Thus, vets hired by large industrial animal organizations will be pressured to approve uses of antimicrobials for disease prevention purposes, in order to make up for crowded, unclean conditions in which the animals are housed. In addition, some veterinarians sell antimicrobials and will face a conflict of interest if they stand to profit from the sales of such antimicrobials. Thus, one cannot expect all veterinarians to provide a meaningful check on indiscriminate preventative uses, especially in the absence of specific rules from the FDA.

FDA could use the five factors to determine whether a specific preventative use is appropriate, but FDA has no statutory authority to ensure that veterinarians consider such

[21] IOM *Op cit.*
[22] Mellon et al. *Op cit.*

factors. FDA should seek the statutory authority to be able to set these five factors, and to require that veterinarians consider them prior to approving antimicrobial use. The FDA should also review the data on existing approvals for disease prevention and determine which constitute judicious use.

Conclusion

We commend FDA for explicitly recognizing that steps need to be taken to ensure the judicious use of medically important antimicrobials in animal agriculture and for developing a policy framework regarding the judicious use of medically important antimicrobial drugs in food-producing animals. We strongly agree with FDA that injudicious use of antimicrobial drugs should be minimized and eliminated, where possible, in order to help minimize antimicrobial resistance development. However, we urge the agency to implement a rulemaking, rather than a Guidance; since the Guidance is voluntary, we do not think it will be effective enough on its own in reducing injudicious use of antimicrobials.

Consequently, we believe the best way to accomplish this goal is to ban all subtherapeutic uses of medically important antimicrobial drugs in food-producing animals. This would mean that, in addition to declaring all uses of antimicrobials for production purpose to be injudicious, all subtherapeutic uses for disease prevention should be declared injudicious as well, since a large majority of antimicrobial use is for disease prevention. Should FDA decide to declare some subtherapeutic uses of antimicrobials for disease prevention as judicious, we feel FDA must set a goal (such as 75%) and a timetable for total reduction of antimicrobials used for disease prevention FDA. In addition, FDA should require use reporting of antimicrobials in animal agriculture, so that progress on such a timetable can be monitored.

Thank you for the opportunity to provide comments on this important matter.

Yours,

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