KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.com

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Docket No. FDA–2011–D–0889: Draft Guidance 213

Comments of Keep Antibiotics Working

Keep Antibiotics Working (KAW), a coalition of health, consumer, agricultural, environmental, humane, and other advocacy groups with more than eleven million supporters, appreciates this opportunity to comment upon the Food and Drug Administration's (FDA) Draft Guidance for Industry #213, "Draft Guidance for Industry on New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions With GFI #209" (hereinafter referred to as Draft Guidance #213). KAW is dedicated to eliminating the inappropriate use of antibiotics in farm animals, a major cause of the rise in antibiotic resistant disease.

Introduction

Draft Guidance #213 instructs industry on the implementation of a policy laid out in another guidance document, Guidance for Industry #209 (hereinafter referred to as Guidance #209). That guidance set forth a policy addressing the antibiotic resistance crisis by encouraging drug sponsors to voluntarily withdraw claims for uses of antibiotics intended to boost production, such as growth promotion and feed efficiency, while allowing approvals for other uses (i.e. disease treatment, disease control, and disease prevention) to stay on the market. The FDA considers production uses of medically important antibiotics to always be injudicious, in contrast to its views on treatment, control, and prevention, which are considered judicious when used appropriately.

As stated in earlier comments on a draft version of Guidance #209[1] and briefly discussed below, KAW doubts that the voluntary approach adopted by the FDA will effectively address the problem of antimicrobial overuse on farms. As a result, we urge the Agency

[1] Comments of Keep Antibiotics Working on Draft Guidance #209, the Judicious Use of Medically Important Antimicrobial Drugs in Food-producing Animals, Docket No. FDA-2010-D-0094 (August 27, 2010) Available from: http://www.keepantibioticsworking.com/new/KAWfiles/64_2_107673.pdf.

to abandon the voluntary approach and instead use its legally mandated authority[2] under the Food, Drug and Cosmetic Act (FDCA) to cancel inappropriate uses of veterinary antibiotics.

If, however, the FDA goes forward with the voluntary plan, we believe that it needs to be improved in the important ways set forth below. Moreover, if the Agency moves to implement its voluntary plan, it should immediately begin to produce evaluations of the safety of medically important antimicrobials so that the Agency will be prepared for the eventuality that companies refuse to participate or do so only in a limited fashion.

Detailed Comments

I. The FDA should abandon the voluntary approach laid out in Guidance #209 and initiate formal cancellation proceedings under its existing authority.

The voluntary approach set forth in Guidance #209 is unlikely to lead to meaningful reductions in veterinary drug use for two interrelated reasons.

First, manufacturers of veterinary antimicrobials, the group whose support is most needed for the plan to work, are not likely to voluntarily give up the profits derived from the sales of veterinary drugs.

Second, even if all of the companies agree to follow the voluntary plan, the health impacts may be minor. Antimicrobial drugs previously used for growth promotion will very likely continue to be used in animal operations in similar amounts and for similarly long periods of time for routine prevention. Currently, as can be seen in Appendix A to these comments, prevention approvals with no limit on duration and the same or only slightly higher doses as production uses are in place for all classes of medically important antimicrobials that have approvals for production.

If the same antibiotics continue to be used at the same or slightly higher dose in the same number of animals for the same duration, the FDA's voluntary policy will yield no public health benefit. This will be the result if, as is likely, disease prevention claims are substituted for production claims. Because the modes of use (long duration and low dose) are the same, there is no scientific rationale for distinguishing between routine prevention and production uses of antibiotics. This is recognized in FDA's Guidance for Industry #152 (hereinafter referred to as Guidance #152), which describes the FDA's recommended method for evaluating the safety of antimicrobial drugs, including restrictions on mode of use. It does not make recommendations on what purposes are safer than others[3]. The eleven studies cited in Guidance #209 as supporting further action to address antibiotic use on farm focus, for the most part, on mode of use and make no distinction as to the purpose of use.[4]

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[2] Food, Drug and Cosmetic Act §512(e)(1) (21 USC §360b(e)(1))

[3] *Guidance for Industry #152, Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*. Table 8 at 25.

[4] Guidance #209 at 15.

KAW anticipates that manufacturers of veterinary antimicrobials will participate in the voluntary plan only to the extent that it does not affect their overall ability to market drugs. KAW anticipates that they will readily remove growth promoter claims for products that have an existing prevention claim of unlimited duration (as Novartis has already done for tiamulin[5]), but likely will not do much more. Officials with the animal pharmaceutical industry group Animal Health Institute have admitted that member companies are likely to market preventive antibiotics as substitutes for production antibiotics and will be unwilling to remove production uses before the new prevention claims have been approved.[6] In addition, Draft Guidance #213 creates a pathway for the approval of new therapeutic claims (which FDA defines to include disease prevention claims) to replace existing production claims.[7] This opens up another avenue for companies to maintain or even increase drug sales.

As envisioned, the voluntary program will take around five to seven years to implement. The public will have little idea of whether the program is working until well into its implementation. Draft Guidance #213 states that the FDA will not evaluate progress on the program until three years after it is finalized. Only then will the FDA consider whether further action is needed.[8] Draft Guidance #213 also indicates that most likely the three-year implementation period will not begin until after rulemaking on changes to Veterinary Feed Directive (VFD) is completed.[9] The rule making on VFD has just begun and could easily take more than five years, with at least two more cycles of public comment and review.

Ironically, FDA has repeatedly stated that it is pursuing this voluntary approach because the legally mandated approach to remove drugs from the market is too resource and time intensive.

Rather than pursue this uncertain and lengthy course, the FDA should abandon the voluntary program and begin the process to formally withdraw approvals of antibiotics under its existing authority for both production and routine disease prevention uses of veterinary drugs. If the FDA were to start today, it likely could complete withdrawals of at least one class of antimicrobials and potentially many more (if companies choose not to contest withdrawals) even before the three year period for implementation of Guidance #213 begins.

II. If the FDA chooses to go forward with the voluntary plan, the FDA should modify Draft Guidance #213 to increase the chance that the plan will succeed, keep the plan from inadvertently weakening the oversight of veterinary antibiotics, and provide transparency to allow the public follow the progress of the program.

A) The *FDA should drop provisions in Draft Guidance #213 establishing a new method for evaluating the safety of antimicrobial drugs. Instead it should recommend that all*

[5] 77 Fed. Reg. 22789 (April 17, 2012).
[6] FDA Week. *Animal Antibiotic Label Changes Hinge on FDA Finalizing Rule, Industry* Says (April 20, 2012).
[7] Draft Guidance #213 at 9.
[8] Draft Guidance #213 at 7.
[9] Draft Guidance #213 at 10.

drugs continue to be evaluated using the method described in Guidance #152. Most importantly, Guidance #213 should uphold the principle in Guidance #152 that drugs found to pose high and medium safety risks not be administered to whole flocks or herds of animals.

Section VI.B of Draft Guidance #213 describes a new approach for addressing microbial safety concerns of antimicrobial drugs that differs from the FDA's current recommended approach found in Guidance #152. Draft Guidance #213 states clearly that this new approach is too be used "in lieu of a complete, qualitative microbial food safety risk assessment,"[10] which is the recommended approach described in Guidance #152.

KAW objects to the approach to addressing microbial safety described in Draft Guidance #213 because it does not incorporate an appropriate consideration of risk as does Guidance #152 and thereby does not include many of the risk based restrictions on conditions of use recommended in Guidance #152. If finalized without change, Draft Guidance #213 will create an alternative method for evaluating veterinary antibiotics' safety with respect to antimicrobial resistance that will allow conditions of use that would not be found safe under Guidance #152.

While Guidance #152 is often described as a risk assessment tool, it actually is a risk management tool that includes three parts: 1) A description of the data that must be provided for a safety assessment; 2) a transparent process for using the data to determine an estimation of risk from the information provided;[11] and 3) a risk management component that includes recommendations on safe conditions of use for products based on the estimated risk. Guidance #152 is very transparent and is highly driven by the data provided, so that risk determinations and recommended safe conditions of use are easy to obtain.

Draft Guidance #213, in contrast to Guidance #152, asks for sponsors to provide the data that could be used for a risk assessment and then skips directly from this to acceptable conditions of use which are simply that "all approved indications should be for therapeutic and/or preventive use only, require veterinary oversight, and restrict use to an explicitly defined duration of dosing."[12]

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[10] Guidance #213 at 11.

[11] Under Guidance #152, a risk assessment and subsequent risk estimation may not always be recommended. The decision not to recommend a risk assessment would be based on a hazard characterization which is a description of the resistant human illness of concern along with information on conditions that influence the occurrence of the resistant illness. It is KAW understands that this provision is included in Guidance #152 to account for the possibility that a specific veterinary drug is not associated with a resistant human illness of concern (i.g. a veterinary drug in a class that is not used in human medicine). If a veterinary drug use does not lead to resistance to any drug used in human medicine, then a risk assessment may not be needed. This is not relevant to the drugs covered by Guidance #213 which are all in classes used in human medicine. In addition, the determination not to carry out a risk assessment is a scientific determination based on a hazard characterization not a general recommendation for all drugs as it is in Guidance #213.

[12] Guidance #213 at 12.

Guidance #213 does not describe what will be done with information provided by sponsors and does not require that sponsors make an estimation of risk, but instead suggests that any new indication meeting the three listed conditions of use (therapeutic/preventive only, prescription/VFD required, defined duration of dosing) will be considered safe.

A basic principle of Guidance #152 is that the higher the risk of a drug, the more restriction on use is needed for the drug to be considered safe.[13] For example, under Guidance #152, recommended safe conditions of use for drugs considered high risk include prescription-only marketing status, restrictions on extralabel use, and low extent of use; on the other hand, a low risk estimate drug may be used over-the-counter with extralabel use allowed and high extent of use.[14] Because the alternative process for safety evaluation created in Draft Guidance #213 does not require a risk assessment or the resulting risk estimation, it provides no basis for determining what restrictions are needed for safe use of a drug. Instead it only includes a subset of the restrictions recommended in Guidance #152, which we assume will be applied to all drugs evaluated using the new process independent of risk.

The list of safe use conditions for veterinary antimicrobials in Draft Guidance #213 (therapeutic/preventive only, require veterinary oversight, restrict use to defined duration of dosing) does not include important restrictions included in Guidance #152 on the number of animals that can be administered antibiotics. It also does not state what defined duration of dosing is acceptable. The list of safe use conditions in Draft Guidance #213 also does not include extralabel use restrictions, post approval resistance monitoring, or pre-approval review by advisory committee – all of which are part of Guidance #152.

The most significant difference between Guidance #152 and Draft Guidance #213 on safe use conditions lies in restrictions on the number of animals that can be treated with antibiotics. Guidance #152 recommends that uses with a risk estimation of high or medium (under which many uses of medically important drugs in feed or water would fall) not be administered to whole flocks or herds.[15] In fact, Guidance #152 recommends no use in groups of animals for drugs with a high risk estimation - so water or feed use in major species would be precluded altogether for these drugs.[16]

High risk is the likely risk estimation for any drug deemed to be critically important for human medicine and will be the estimation for many uses of drugs considered highly important as well. Critically important drugs currently allowed in feed include macrolides and sulfonamides, and this list may be expanded in the future.[17]

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[13] Guidance #152 at 25.
[14] Guidance #152 Table 8 at 25.
[15] Guidance #152 Table 7 at 23 and Table 8 at 25.
[16] Guidance #152 Table 8 at 25. The table does not include VFD as an option for high risk drugs consistent with the recommendation that these drugs not be administered to groups of animals.
[17] Guidance #152 Appendix A.

In addition, while Draft Guidance #213 does state that drugs approved under the new process should have a defined duration of use,[18] it does not state what that duration should be. Under Guidance #152, the longest duration recommended for a medium or high risk estimation drug is 21 days.[19] As noted above, Draft Guidance #213 also does not mention several other safe conditions of use recommendations included in Guidance #152.

Even more significant is that the FDA is changing what it means to be safe with respect to resistance and is undermining its own current risk based approach. It does so by officially recognizing an alternative approach to determining safety that does not require risk assessment and that leads to different outcomes from Guidance #152. Sponsors will have the choice between using the risk based approach in Guidance #152 and the alternative approach in Draft Guidance #213 where risk is not considered. This scenario means the sponsor can instead negotiate for conditions of use that will be less restrictive than for Guidance #152.

Once Draft Guidance #213 becomes finalized - indicating that FDA has determined that this approach meets the legal requirements of safety under the FDCA - it is difficult to see how the Agency will be able to argue that this new approach is not appropriate for other drug approvals as well.

KAW understands that both Guidance #152 and Guidance #213 are guidance and therefore alternative approaches could be used by a sponsor seeking a new drug approval. This is correct, but any sponsor wishing to use an alternative approach would have to demonstrate that the alternative approach meets the legal definition of safety with respect to the FDCA and the FDA would need to make a determination that the method was acceptable. If on the other hand, the sponsor chooses to use an approach recommended by the FDA, then it is assumed to meet the legal safety standard and the sponsor would not need to justify the method.

Once Guidance #213 is finalized, there will be two separate methods that the FDA has determined can be used to evaluate the safety of antimicrobials used in food-producing animals as required by FDCA. These two methods would likely result in different findings of safety for the same product. One will be risk based and the other will be based on a predefined list of use conditions independent of risk.

In sum, Draft Guidance #213 as written leaves the door open for new approvals for routine flock-wide and herd-wide preventive uses and would likely eventually replace the stronger standards in Guidance #152 with weaker standards. The provisions establishing that process should be dropped from the draft. Instead, final Guidance #213 should clearly state that all new approvals continue to be evaluated under Guidance #152.

B) Guidance #213 should restrict injudicious uses of antibiotics for disease prevention as well as production and include a recommendation that sponsors modify prevention

[18] Guidance #213 at 12.
[19] Guidance #152 Table 7 at 23 and Table 8 at 25.

claims to bring them in line with the safe use recommendations on extent of use in Guidance #152.

The FDA, in both Guidance #209 and Draft Guidance #213, acknowledges that "the 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 such drugs to individual animals or targeted groups of animals."[20] Both the number of animals treated and the duration of treatment are important in assessing the risk of using a drug. As stated in Draft Guidance #213, "giving antimicrobial drugs to food-producing animals at low levels for long periods of time in large numbers of animals may contribute to antibiotic resistance."[21] Yet the FDA in Draft Guidance #213 recommends no restrictions on the number of animals treated or on other important factors such as duration of treatment or the dose given.

KAW is concerned because it is very likely, as discussed above, that drugs sponsors will continue to sell the same drugs previously sold for production purposes for routine disease prevention. Appendix A to these comments, which lists medically important antimicrobials approved for production and disease prevention in feed, clearly shows that for all classes of medically important antibiotics there are existing prevention approvals that can be continuously administered to entire herds or flocks. While there is variation between species and production class in which prevention drugs are available, for each of the top three food producing species (i.e. cattle, chickens, and swine) there are at least three options for prevention approved for continuous use at the same or only slightly higher dose than that approved for production purposes.

As we discussed in the introduction above, there is no scientific basis for considering herd or flock wide use of medically important antimicrobials for unlimited duration for disease prevention to be any safer than for production purposes. This type of use is inconsistent with the extent of use limitations recommended in Guidance #152 and is even inconsistent with the weaker use limitations in Section VI.C in Draft Guidance #213 because there is no defined duration of dosing. FDA recently recognized the qualitatively greater risk that occurs when antimicrobials are used for disease prevention in its recent prohibition on extralabel use of the antibiotic ceftiofur. In that case, the FDA prohibited extralabel use of ceftiofur for disease prevention while allowing it to continue to be used extralabel for disease treatment.[22]

KAW recognizes that there are judicious preventive uses of antibiotics, but these uses are usually short term.

KAW recommends that Guidance #213 include a section describing what changes sponsors of antimicrobials with existing prevention claims should make to align their products with the safe conditions of use described in Guidance #152. Specifically, high

[20] Guidance #209 at 18 and Draft Guidance #213 at 7.
[21] Draft Guidance #213 at 11.
[22] 77 Fed. Reg. 735 (January 6, 2012).

and medium risk drugs should not be administered to whole herds or flocks of animal and should have a defined duration of use that is less than 21 days.

C) Guidance #213 should include a plan for periodically publishing the number of sponsor submissions for label changes and applications for new therapeutic claims, the number of completed label changes, and the number of products not currently in compliance with recommendations.

It is absolutely essential that the FDA make frequent public reports on the implementation of the program outlined in Draft Guidance 213 for the following reasons:

- The FDA's plan to address antimicrobial overuse is completely dependent on voluntary action by the regulated industry, with the potential for companies to stop participating at any point;
- All discussion between sponsors and the FDA about specific drugs are behind closed doors;
- There is the potential for significant delays due to the vagaries of rule making; and
- The FDA has made clear that any further actions that will be needed in the case of sponsor's non-participation could take significant additional time.

KAW recognizes that confidentiality restrictions limit what information the FDA can provide on pending approvals, including those to be submitted under Guidance #213. However, the FDA routinely reports on the number and nature of pending animal drug applications as part of the Animal Drug User Fees Act Performance Reports.[23] KAW asks that similar information be provided to the public to monitor the performance of the FDA's voluntary plan on antibiotics

Draft Guidance #213 says that the FDA will only begin monitoring compliance by the industry "Upon issuance of the final guidance."[24] This issuance could be several years away, as the Draft Guidance also says that the issuance will coincide with the implementation of the final VFD rule.[25]

KAW believes that the FDA should inform the public now -- not in several years – whether the drug companies are voluntarily asking for changes in their labels. Specifically, KAW recommends that, beginning in early 2013, the FDA make public the total number of new animal drug products the Agency believes is not aligned with Guidance #209, along with the number of sponsors that have products that are not aligned. This information is needed as a baseline to determine whether progress is actually being made.

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[23] ADUFA Performance Reports. Available from: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ADUFA/default.htm

[24] Draft Guidance #213 at 7.

[25] Draft Guidance #213 at 8.

Then, every three months the FDA should provide updated information on: 1) the number of companies that have agreed to participate in the voluntary process, 2) the number of supplemental new animal drug applications submitted, 3) a cumulative list of product changes that have been finalized, and 4) the number of products not yet in alignment with Guidance #209. The list of supplemental applications and finalized changes should be broken out in terms of removal of production claims, change in marketing status, and new therapeutic indications.

This information is needed so the public can determine whether or not the plan is working and may also help motivate pharmaceutical companies to participate. Information on the number of products not yet in alignment is as important for measuring progress as the information on the number of changes that have been made.

D) FDA should institute an evaluation plan for Guidance #213 that sets goals for desired reductions in antimicrobial use and levels of resistance in monitored bacteria, along with a menu of possible agency responses if the goals are not met.

While implementation of the plan is essential for it to have any impact, the goal of the plan is to protect human health from resistance that occurs because of antibiotic use in food-producing animals. For there to be any change in the risk of resistance, there must be reductions in antibiotic use.

For this reason, KAW asks that the FDA institute an evaluation plan and include it within final Guidance #213. The plan should set goals for the program in three areas: 1) antibiotic use, 2) antimicrobial resistance in bacterial isolates from the food system, and 3) antimicrobial resistance in human pathogens. It should also include a timeline for meeting the goals as well as options to be taken if the goals are not met.

Review and evaluation of actions taken is an essential part of risk management. Evaluation is especially important in this case where the voluntary nature of the program means that companies can choose to only make changes that do not affect antibiotic use (i.e. substitution of routine prevention uses for production uses).

Reductions in antibiotic use can be monitored by reviewing drug distribution data collected under Section 105 of the Animal Drug User Fee Amendments of 2008 (ADUFA), but should include other available sources of data. Goals related to reductions in antimicrobial resistance in bacterial isolates can be monitored by data collected through the National Antimicrobial Resistance Monitoring System (NARMS). Given the very long time that antibiotics have been overused in food animals, likely it will take some time for changes in antibiotic use to be reflected in resistance levels. Therefore, the intermediate goal of reductions in antibiotic use is absolutely necessary. The monitoring and review plan also must identify potential steps to be taken if goals are not met.

E) Guidance #213 should be revised to apply to all antibiotics in drug classes used in human medicine rather than those drugs identified in 2003 in the Appendix to Guidance #152.

Section III of Draft Guidance #213 explains that for the purpose of the guidance "medically important" refers to those drugs listed in the Appendix to Guidance #152,[26] but, on close inspection of the language, it is unclear which drugs are actually covered. The Appendix to Guidance #152 for the most part does not rank individual drugs, but instead ranks classes of drugs and then includes some drugs used in human medicine under each class. Draft Guidance #213 does not refer to drugs classes, but instead only refers to listed drugs.

At the very least, the FDA should clarify in final Guidance #213 that all drugs in the same classes as drugs listed in the Appendix to Guidance #152 are considered "medically important" for purposes of implementing the guidance. If only individual drugs are considered instead of classes, then several important antibiotics - including the macrolide tylosin, the tetracycline oxytetracycline, and even the fluoroquinolone enrofloxacin - would not be considered "medically important" by the FDA. Such a mistake would occur because they are not listed in Appendix A to Guidance #152, even though they are known to share cross-resistance with drugs listed in the Appendix. The FDA has already placed all antimicrobials used in food producing animals into classes for purposes of reporting antimicrobial drugs sales and distribution under reporting requirements in Section 105 of the Animal Drug User Fee Amendments of 2008.[27] KAW recommends that the FDA use those classifications when determining the medical importance of individual drugs.

However KAW also recommends that a simpler and more comprehensive approach would be to consider all antimicrobials in classes of antibiotics used in human medicine as medically important with respect to Guidance #213. This approach is consistent with the World Health Organization ranking of medically important antimicrobials, which classifies all drugs used in human medicine as important.[28]

According to our analysis of the drugs listed in Appendix A to Guidance #152, the only change that would occur if all classes of drugs used in human medicine are considered medically important opposed to only those in classes listed in Guidance #152, would be that the pleuromutilin feed additive tiamulin would be added to the list of medically important drugs.[29] Tiamulin is not currently ranked in Guidance #152 because the related human drug retapamulin was only approved in 2007 after the guidance was finalized. The

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[26] Draft Guidance #213 at 4.

[27] *2010 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*. Available from:
http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm

[28] *Critically Important Antibacterial Agents for Human Medicine for Risk Management Strategies of Non-human Use.* Report of a WHO working group consultation, 15 - 18 February 2005, Canberra, Australia. http://www.who.int/foodborne_disease/resistance/FBD_CanberraAntibacterial_FEB2005.pdf

[29] For most drugs, Appendix A of Guidance #152 lists drugs by antimicrobial class. For a few drugs, the class is not given. For example, clindamycin is listed but it is not placed in the lincosamide class which includes the feed additive lincomycin. Similarly the polypeptide polymixin b is listed but not the polypeptide feed additive bacitracin. There is some ambiguity as the combination of trimethoprim with sulfamethazine is considered critically important but there is no ranking for a sulfonamide alone. We assume that FDA considers all of these drugs to be medically important because they are in the same classes as other medically important antibiotics but this needs to be clarified.

Appendix has never been updated. Unless FDA has a specific reason to exclude tiamulin from Guidance #213, despite evidence that there is cross resistance between pleuromutilins and other medically important classes of drugs,[30] it would make more sense to consider all drugs in all classes used in human medicine as medically important.

F) FDA should make clear that Guidance #213 is not intended to extend approvals to new species or new production classes.

Section VI.B of Draft Guidance #213, which covers what a sponsor must do to add a new therapeutic claim to a drug currently approved for production purposes under "Chemistry, Manufacturing, and Controls," describes what a sponsor must do for medicated feeds in a "species not currently approved."[31] Draft Guidance #213 states that Section VI.B is included to address situations where "there could be a therapeutic benefit associated with a production use of a drug."[32] If the purpose of section VI.B is as stated, to address cases where an existing production claim is actually providing a therapeutic benefit, then there is no need to provide guidance on medicated feed for "species not currently approved." The existing production claim could not provide a benefit in a species for which the drug is not approved. Guidance #213 should clarify that the procedure laid out in Section VI.B should not be used to add therapeutic claims for species that do not already have an approval for production purposes. Sponsors seeking approvals for new uses of drugs in new species should use the normal approval process for new animal drugs rather than the procedure described in Draft Guidance #213.

III. If FDA moves forward with the voluntary program, it should immediately begin to produce evaluations of the safety of medically important antibiotics so that the Agency will be prepared for the likely result that companies refuse to participate or participate only in a limited fashion.

As we stated in Section I of these comments, KAW believes it is likely that the program will not succeed and should not be pursued. The FDA has the authority and obligation under the FDCA to cancel drugs found to be unsafe and it should set about doing that as soon as possible. If the Agency goes ahead with the voluntary program, it should produce evaluations of the safety of medically important antibiotics in parallel with the voluntary process.

The Agency may not know until near the end of the process whether the voluntary plan is working at all. Companies have strong incentives to wait until after they see what the FDA is willing to offer in the way of new approvals before they decide whether to forego existing approvals. This has the potential to create serious market distortions if there is uneven participation in the program between different sponsors, and could further reduce the likelihood that the program will succeed.

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[30] Malbruny et al. 2011. Cross-resistance to lincosamides, streptogramins A, and pleuromutilins due to the lsa(C) gene in Streptococcus agalactiae UCN70. Antimicrob Agents Chemother.55 (4):1470-4; Miller et al. 2008. Linezolid and tiamulin cross-resistance in Staphylococcus aureus mediated by point mutations in the peptidyl transferase center. Antimicrob Agents Chemother. 52(5):1737-42.

[31] Draft Guidance #213 at 11.

[32] Draft Guidance #214 at 9.

In the likely eventuality that the voluntary process does not produce the intended results, the FDA should be ready to initiate cancellation proceedings immediately. Such a step will require up-to-date safety evaluations from the outset. The FDA should begin now to evaluate the safety of medically important antimicrobials used in feed and water, determining which uses (production, prevention, or otherwise) create a public health risk.

IV. Where changes in production practices could alleviate the need for preventive or therapeutic uses of antibiotics, the FDA should not consider those uses as judicious and work with industry to change them.

Draft Guidance #213 describes what the FDA considers to be appropriate prophylactic use.[33] This description fails to include any mention of modifying production practices that necessitate routine preventive use. The example of necrotic enteritis prevention is given, but Draft Guidance #213[34] fails to mention non-antimicrobial interventions that can prevent necrotic enteritis, such as litter management, use of appropriate diets, non-medically important antimicrobials, and non-antimicrobial feed additives.[35] Similarly, there is more evidence supporting the use of the management practice preconditioning (delaying transport for a set period of time after weaning or castration) to successfully prevent bovine respiratory illness than for preventive oral antimicrobials after transport in beef cattle.[36] It is not in the interest of public health to allow routine flock or herd wide antimicrobial use when changes in production could eliminate the need for the antimicrobial use in the first place.

Conclusion

KAW urges the Agency to abandon the voluntary approach and instead use its legally mandated authority under the Food, Drug and Cosmetic Act (FDCA) to cancel inappropriate uses of veterinary antibiotics.

If, however, the FDA chooses to go forward with the voluntary plan, we strongly believe that it needs to be improved in five key ways:

1) Drop provisions establishing a new drug safety evaluation process;

2) Align preventive use claims with the risk management principles of Guidance #152;

3) Make the Guidance #213 process more transparent;

4) Create goals for the program and take additional steps if they are not met; and

5) Revise the guidance to consider all veterinary drugs used in human medicine as medically important for purposes of applying Draft Guidance #213.

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[33] Draft Guidance #213 at 6.
[34] Draft Guidance 213 at 6.
[35] Williams. 2005. Intercurrent coccidiosis and necrotic enteritis of chickens: rational, integrated disease management by maintenance of gut integrity. Avian Pathol. 34(3):159-80.
[36] Taylor et al. 2010. The epidemiology of bovine respiratory disease: What is the evidence for preventive measures? Can Vet J. 51(12):1351-9

If the Agency moves to implement this voluntary plan, it should also begin to immediately produce evaluations of the safety of medically important antimicrobials so that the Agency will be prepared for the eventuality that companies refuse to participate or participate only in a limited fashion.

Whatever approach the FDA chooses to address the problem of resistance resulting from antibiotic use in food producing animals, the Agency must do more to promote practices that reduce the need for antibiotics in the first place, whether for production, prevention or treatment. Management systems that routinely administer antibiotics because they ignore other interventions such as improving diets or minimizing stress should not be condoned.

The FDA has long delayed addressing the risks from the mass medication of food-producing animals. It is hard to see this plan as anything other than yet another delay. In the meantime, we are fast approaching a post antibiotic era in which many antibiotics will no longer be effective in treating animal and human disease. Clearly, animal use of antibiotics is a major factor contributing to the problem, and the crisis of antibiotic resistance is at the point where we should be doing whatever we can to confront it. Reducing the flow of resistance from the farm must be an essential part of addressing this critical public health problem.

Thank you for considering our comments.

Respectfully submitted,

Steven Roach
Public Health Program Director
KAW Member Organization Food Animal Concerns Trust

Appendix A: Overlap between production and prevention uses in medically important antibiotics in feed

Antimicrobial Class, Drug, and Medical Importance	Federal Code	Chicken		Turkey		Swine		Cattle	
	21 CFR 558	**Production**	**Prevention**	**Production**	**Prevention**	**Production**	**Prevention**	**Production**	**Prevention**
Aminoglycosides - Highly									
Neomycin and oxytetracycline	455	10 to 50 g/ton	100 to 500 g/ton 14 days	10 to 50 g/ton	100 to 200 g/ton 14 days	10 to 50 g/ton	10 mg/lb 14 days	75 mg/head/day	75 mg/head/ day No limit
Lincosamides - Highly									
Lincomycin	325	2-4 g/ton	2 g/ton No limit			20 g/ton	40-200g/ton No limit < 100 g/ton		
Macrolides - Critically									
Erythromycin	248	4.6-18.5 g/ton	92.5 & 185 g/ton 14 days	9.25-18.5 g/ton	92.5 & 185 g/ton 8 days	9.25 to 64.75 g/ton		37 mg/head/ day	
Oleandomycin	435	1 to 2 grams		1 to 2 grams		5 to 11.25			
Tylosin	625	4-50 g/ton	800-1000 g/ton 5 days			10-100 g/ton	40-100 g/ton No limit		8 to10 g/ton No limit
Tylosin and sulfamethazine	630					100 and 100 g/ton	100 and 100 g/ton No limit		
Penicillins – Highly									
Penicillin	460	2.4 to 50 g/ton		10 to 50 g/ton		10 to 50 g/ton			
See also combination with chlortetracycline									
Pleuromutilins - not rated									
Tiamulin	600					10 g/ton	35 g/ton No limit		
Polypeptides - Highly									
Bacitracin	76, 78	4-50 g.ton	50 g/ton No limit	4-50 g.ton	200 g/ton No limit	10 -30 g/ton	250 g/ton No limit	35-70 mg/head	70 mg/head No limit

Streptogramins – Highly									
Virginiamycin	635	5-15 g/ton	20 g/ton No limit	10 to 20 g/ton		5-10 g/ton	25, 50, 100 g/ton No limit	11-22.5 g/ton	13.5 to 16 g/ton No limit
Sulfonamides – Critically									
Sulfaquinoxaline.	586		Coccidiosis No limit		Coccidiosis No limit				
Sulfadimethoxine and ormetroprim	575		Coccidiosis No limit		Coccidiosis No limit				
See also combinations with chlortetracycline and tylosin									
Tetracyclines - Highly									
Chlortetracycline	128	10-50 g/ton	100-500 g/ton 14 days	10-50 g/ton	200-400 g/ton 14 days	10-50 g/ton	50-400 g/ton No limit < 100 g/ton	70 mg/head	70 mg/head No limit
	140							350 mg/head per day 28 days	
Chlortetracycline, procaine penicillin, and sulfamethazine.	145					100/50/100 g/ton	100/50/100 g/ton No limit		
Chlortetracycline, sulfathiazole, penicillin	155					100/50/100 g/ton	100/50/100 g/ton No limit		
Oxytetracycline	450	10 to 20 g/ton	100 to 500 g/ton 14 days	10 to 50 g/ton	100 to 200 g/ton 14 days	10 to 50 g/ton	10 mg/lb 14 days	75 mg/head/day	75 mg/head/ day No limit

Color Code for Table	No prevention indication for drug in species	Production and prevention dose overlaps and no specified duration for prevention	Prevention dose is higher than for production in species, may have specified duration

Drug dose, duration, and indications from Code of Federal Regulations http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title21/21cfr558_main_02.tpl
Drug classes from ADUFA summary data reports http://www.fda.gov/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/ucm042896.htm
Drug importance from FDA Guidance #152 http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf