Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
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RE: GFI 213: 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 [Docket No. FDA-2011-D-0889]

The Center for Science in the Public Interest (CSPI) appreciates the opportunity to comment on the Food and Drug Administration’s (FDA) Draft Guidance for Industry #213, “New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: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 (GFI 213).” 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 850,000 subscribers to its Nutrition Action Healthletter and by foundation grants. CSPI is a member of the Keep Antibiotics Working coalition (KAW), a group of health, consumer, agricultural, environmental, humane, and other advocacy groups with more than 10 million members dedicated to eliminating the inappropriate use of antibiotics in farm animals, a major cause of antibiotic resistance.

As part of this commitment, CSPI has been closely monitoring U.S. progress on this critical public health issue. We have addressed antibiotic resistance from multiple angles, including petitioning the U.S. Department of Agriculture (USDA) to declare several strains of antibiotic-resistant Salmonella as adulterants, thus making products containing these strains illegal in commerce.1 We also participate in international standard setting committees on antibiotic issues, including providing expert participation on the World Health Organization’s Expert Advisory Group on Integrated Surveillance of Antimicrobial Resistance. This group publishes the list of Critically Important Antimicrobials for Human Medicine and assists WHO on matters related to antimicrobial usage monitoring, antimicrobial resistance surveillance, and capacity building for antimicrobial resistance monitoring. In addition, CSPI has worked with the Trans Atlantic Consumer Dialogue (TACD) to bring the issue of antimicrobial resistance to the foreground on both sides of the Atlantic. At the June 2012 TACD 13th Annual Meeting, CSPI spoke on antimicrobial resistance and presented the issue before EU and US government officials. TACD’s Resolution on Antimicrobials in Animal and Food Production calls for all antimicrobial usage in animals to be subject to veterinary prescription and that the use of critically important drugs to human medicine in animals be significantly reduced or eliminated.

1 See http://cspinet.org/new/pdf/cspi_petition_to_usda_on_abr_salmonella.pdf
CSPI has also published a White Paper chronicling the urgent public health crisis of antibiotic resistance through outbreak data.\(^2\) *Antibiotic Resistance in Foodborne Pathogens: Evidence of the Need for a Risk Management Strategy* documents a total of 38 foodborne outbreaks that occurred between 1973 and 2011 in which the bacteria identified were resistant to at least one antibiotic. These outbreaks illustrate the link between foods, mostly of animal origin, and outbreaks of antibiotic-resistant pathogens in humans. Cataloging foodborne illness outbreaks is a critical step in documenting the link between administering antibiotics to food-producing animals and human illness as it relates to antibiotic resistance in infectious diseases.

CSPI has several major areas of concern with GFI 213. In addition to those issues delineated herein, CSPI shares the concerns expressed in the KAW comments.

I. **The voluntary nature of GFI 213 severely hinders its effectiveness.**

As a threshold matter, CSPI has grave concerns with the voluntary approach that FDA has selected for dealing with antibiotic misuse in food production. We continue to assert that the time has long passed for FDA to take resolute action to arrest this problem. Notably, in March, a federal court ruled that FDA must begin withdrawal proceedings for penicillin and tetracyclines in animal feed unless drug manufacturers prove that such uses are safe.\(^3\) In June, that court directed FDA to reexamine its decision to deny two Citizen Petitions filed in 1999 and 2005, which asked the FDA to stop the unnecessary use of medically important antibiotics on livestock. As a plaintiff in the underlying suit, CSPI agrees with the court that FDA bears the responsibility for mandating the removal of these drugs from animal production.

CSPI believes that the voluntary approach favored by FDA is likely to fail. It is unlikely that the animal drug industry will voluntarily change its business model, and equally unlikely that animal food producers will voluntarily change their practices of animal husbandry—particularly those such as overcrowding—that give rise to the conditions requiring antibiotic use. We find it far more likely—and just as disturbing—that the industry will either ‘wait out the clock,’ counting on FDA’s lengthy procedures to negate its intent, or simply find ways around the new guidelines, such as shifting an existing use from “growth promotion” to “prevention” without any meaningful change in practice. We are concerned that GFI 213 actually assists the industry by creating a pathway for the approval of new therapeutic claims to replace existing production claims.

In fact, the voluntary plan outlined by FDA does not adequately address the issue of preventive use of antibiotics, focusing instead on growth promotion (despite the reality that many of the same drugs are used for both purposes). The agency introduces its guidance by asserting that “FDA believes that production use indications such as ‘increased rate of weight gain’ or ‘improved feed efficiency’ are no longer appropriate for the approved conditions of use for medically important antimicrobial drugs. In contrast, FDA considers uses that are associated with the treatment, control, and prevention of specific diseases to be therapeutic uses that are necessary for assuring the health of food-producing animals.”

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CSPI notes that if the same antibiotics continue to be used in the same manner, albeit for a different purpose, there will be little substantive public health benefit.

We urge the agency not to fall victim to magical thinking about the readiness of the industry to sacrifice the production methods they have relied on for several decades. FDA needs to recognize that progress on antibiotic use may not be possible until the agency mandates it.

II. **GFI 213 is not transparent enough to allow stakeholders to track its effectiveness.**

Under the proposal, drug sponsors are urged to notify FDA of their intention to comply with the voluntary guidelines within three months. However, nowhere does the agency discuss its plans to share that information with stakeholders. Such transparency is critical for stakeholders to monitor compliance in real-time. It is simply not acceptable for the public to have to wait until the completion of an FDA review (which won’t begin until after three years of implementation) to gain an understanding of the actions or inactions of the drug companies that control these essential antibiotics.

In keeping with the goal of transparency underpinning the Food Safety Working Group established by President Obama, and in recognition of the urgency of the problem of antibiotic resistance, FDA should release detailed information to stakeholders and consumers at the close of that initial three-month period, including the names of companies that have committed to implementing the guidance and what products are included in that notification, as well as the names of companies that have not complied with FDA’s requested notification and the relevant drugs that those companies bring to market.

If FDA finds companies that have failed to comply with the request for notification, the agency should publicly release its strategy for bringing all industry members into compliance with the guidance. These announcements should be made immediately after the three-month deadline expires, and the agency’s commitment to publicizing compliance intent should serve as an additional driver for industry to participate.

After these announcements, FDA should publish periodic reports informing stakeholders of compliance rates, including progress reports on already-committed companies and updates on efforts to induce compliance in others. These reports should be issued on a regular schedule, such as every 90 days.

Consumer groups such as CSPI and the members of the KAW coalition should have an opportunity to analyze the compliance data that is available to the agency so as to better advise the agency and consumers of whether the voluntary effort is showing signs of success. Without this transparency, FDA only signals to the industry that it intends to delay mandatory action as long as possible, without allowing consumers and stakeholder organizations to identify companies that may place their corporate or economic interest above the need to protect public health from harmful foodborne pathogens.

III. **The timeline for action under GFI 213 is too long at the outset, and subject to additional delay.**
The timeline for implementation referenced in GFI 213 does not reflect the urgency of the threat from antibiotic resistance. GFI 213 states that FDA will evaluate progress on the program three years after final guidance is released, and only then will the agency consider further action. GFI 213 also states that its implementation will likely be delayed until after final rulemaking on the Veterinary Feed Directive: “Although FDA is committed to completing this rulemaking process within the 3-year timeframe for implementing the changes discussed in this draft guidance, FDA is prepared to extend the timeframe, as necessary, to ensure that it coincides with the implementation of the revised VFD requirements.”

We have concerns that, given FDA’s pace of completing rulemaking, this process could linger for several years, if not more. FDA itself acknowledges that rulemaking is time-consuming, and has used that reasoning to avoid rulemaking on the specific issue of antibiotic withdrawals, such as those requested in CSPI’s 1999 petition. In the meantime, the problem of antibiotic resistance will continue to grow, putting consumers at risk from the resulting hard-to-treat infections.

Given FDA’s limited resources and the urgent public health need to address the growing problem of antimicrobial-resistant pathogens in our food supply, CSPI strongly recommends that the agency follow the edict of the federal court without delay or appeal, and begin initiating withdrawal proceedings for penicillin and tetracyclines. The agency must initiate mandatory action to protect consumers, rather than waiting several years to see if a voluntary approach makes significant progress.

IV. **FDA should maintain Guidance for Industry 152 as the method for evaluating the safety of antibiotics.**

In GFI 213, FDA has proposed a new approach for evaluating the safety of antibiotics that differs from the recommended approach described in Guidance for Industry 152: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern (GFI 152). GFI 152 sets forth a transparent process for evaluating and determining risk, and recommends safe conditions of use appropriate to different risk estimates. That tool provides a fairly strong framework for estimating risk-- unlike the proposal under GFI 213.

GFI 213 expressly states that sponsors of current approvals for medically important antibiotics in food and water should provide information about the drug to the Agency “in lieu of a complete, qualitative, microbial food safety risk assessment”. GFI 213 then instructs sponsors on conditions of use. This process weakens significantly the current risk assessment safeguards, where a sponsor is

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6 See. GFI 213, pp. 11-12.

To address the Agency’s antimicrobial resistance concerns and in lieu of a complete, qualitative, microbial food safety risk assessment, firms should discuss with CVM the type of information to submit with their application. This information may include, but is not limited to:

1. Basic information on the subject antimicrobial new animal drug, including information on mechanisms of action, spectrum of activity, resistance mechanisms, transfer of resistance, pharmacokinetics and/or pharmacodynamics if known, proposed conditions of use and how these could influence resistance development, and information on susceptibility among bacteria of human health concern;
required to determine an estimate of risk and from there determine the conditions of safe use based on recommendations from the agency. The current framework (GFI 152) is transparent and data-driven so that outcomes and safe conditions of use are easy to obtain. GFI 213, in contrast, does not provide detail on how the agency will make decisions, but implies instead that meeting the listed conditions (for therapeutic/preventive use only, requiring veterinary oversight, and restricting duration of use) will be sufficient for determining safety.

A risk assessment is not always required under GFI 152. If a specific veterinary drug is not associated with a resistant human illness of concern (i.e. a veterinary drug in a class that is not used in human medicine) then a risk assessment may not be needed. However, all the drugs covered by GFI 213 are used in human medicine. Further, whether or not to perform a risk assessment is a decision that should be made based on the hazard profile of an individual drug-- not a sweeping generalization such as the one in GFI 213.

In addition to requiring no determination of risk, the new method for safety analysis described in Guidance 213 differs from the current method by eliminating many of the safeguards on use included in GFI 152.

CSPI has additional concerns with GFI 213 when compared to GFI 152 because the former does not include restrictions on the number of animals that can be treated at one time. GFI 152 recommends that drugs with a high (category 1) or medium (category 2) risk estimation-- which accounts for many medically important drugs currently used in animal production-- not be administered to whole flocks or herds (GFI 152, Tables 7 and 8). In fact, under GFI 152 for high risk uses (category 1 - the likely risk estimation for any critically important drug for use in a major species), any use in groups of animals is not recommended, so water or feed use would be precluded altogether. This provision of GFI 213 could result in new approvals for routine flock-wide and herd-wide preventive uses (in lieu of improved animal husbandry to reduce the risk of illness) that would be inconsistent with the recommendations for safe use in GFI 152.

V. Conclusion

CSPI believes that the responsibility for arresting the growth of antibiotic resistance lies equally with the agency and the industry. Unfortunately, animal production practices are deeply rooted in a tradition of injudicious use of antibiotics, and that use continues to threaten public health. The urgency of the issue demands that FDA take steps to intensify its approach to this issue, including by making GFI 213 a mandatory requirement for drug companies with a much shorter timeframe and beginning penicillin and tetracycline withdrawal proceedings without delay.

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(2) Information on the use of the subject antimicrobial new animal drug in or on the feed or water of food-producing animals, focusing on numbers of animals treated, class, consumption rates for food products from treated animals, and rates of contamination by bacteria of human health importance;
(3) Information on the use of the subject antimicrobial drug or drugs similar to it in human medicine, including a discussion on how loss of susceptibility of organisms of human health concern to the subject antimicrobial drug or drugs could impact human clinical medicine;
(4) Information detailing how FDA’s general elements of judicious use discussed in section II have been addressed. Specifically, 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. FDA considers these measures to be significant risk mitigations consistent with the goals of GFI #152.
Sincerely,

[Signature]

Sarah Klein
Staff Attorney, Food Safety Program