November 19, 2012

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

RE: Docket No. FDA–2012–N–0447

Comments on the Food and Drug Administration's Advanced Notice of Proposed Rulemaking (ANPR) on Antimicrobial Animal Drug Sales and Distribution Reporting

The undersigned groups, including Keep Antibiotics Working (KAW)[1], appreciate this opportunity to comment on the Food and Drug Administration's (FDA) efforts to both collect and publicly report on antimicrobial use in food producing animals.[2]

FDA has asked for comment on three specific areas of data collection and reporting: A) how can animal drug sponsors both practically and accurately provide separate sales and distribution information for each species; B) how best can FDA compile and present summary information collected under Section 105 of ADUFA; and C) what alternative methods for assessing antimicrobial use can the Agency employ within its existing authority. We shall respond to all three areas below.

Introduction:

The FDA should avoid using this ANPR to further delay collecting and publishing better data on antimicrobial use in food animals.

It is beyond dispute that antimicrobial use is a primary driver of the formation and spread of antimicrobial resistance. In 2001, the Union of Concerned Scientists, a KAW member organization, published the first comprehensive estimates of antimicrobial use on farms and recommended that the FDA, along with other federal agencies, create a system to collect data on this use.[3]

Since then, KAW has consistently asked for the collection of these data specific to food animals, as have other organizations.

The collection of veterinary drug use data is widely recognized as being an important tool for the management of antimicrobial resistance. It is as a top priority in the Public Health

[1] Keep Antibiotics Working, a coalition of health, consumer, agricultural, environmental, humane, and other advocacy groups with more than eleven million supporters, is dedicated to eliminating the inappropriate use of antibiotics in farm animals, a significant contributor to the rise in antibiotic resistant disease.

[2] 77 Fed. Reg. 44177 (July 27, 2012).

[3] Union of Concerned Scientists (2001). *Hogging It: Estimates of Antimicrobial Abuse in Livestock.* Available from: http://www.ucsusa.org/food_and_agriculture/science_and_impacts/impacts_industrial_agriculture/hogging-it-estimates-of.html

Action Plan of the 2001 Interagency Task Force on Antimicrobial Resistance, created by federal agencies (including the FDA) to better address the growing threat of antimicrobial resistance.[4] The collection of drug use data is also recommended by the World Health Organization[5] (WHO) and the World Organization for Animal Health[6] (OIE). In a 2007 review of the National Antimicrobial Resistance Monitoring System (NARMS), the FDA's Science Advisory Board recommended that drug use data be integrated with microbiological data, and stated that the lack of drug use data "represents a critical barrier for NARMS to achieve its objectives and further utility."[7]

Despite the clearly recognized need for information on antimicrobial use, the FDA took no steps on its own to collect such data. So in 2008 Congress stepped in and enacted section 105 of Animal Drug User Fee Amendments (ADUFA).[8] Section 105 requires animal drug companies to report by March 31 of each year the annual sales of antibiotics in the previous year by container size, strength, and dosage form, a listing of the target animals, and the approved ways each antibiotic can be used. The FDA is charged with making summaries of these data public. Two reports of such data, covering animal drugs sales in 2009 and 2010, have been prepared and released to date.

While collection of drug sales and distribution data under Section 105 of ADUFA is an improvement, the data published to date lack important features limiting their usefulness for managing the public health risk from antimicrobial resistance. Namely, the FDA's reports fail to set forth the amounts of antibiotics sold for use in particular animal species and for specific purposes. A 2011 report by the Government Accountability Office (GAO) recognized these limitations and recommended that federal agencies collect "detailed data on antibiotic use in food animals, including the species in which antibiotics are used and the purpose for their use" in order to track the effectiveness of FDA's efforts to curb antibiotic resistance.[9]

The FDA has also failed to make public important information it possesses, such as the route of administration and amounts of antimicrobials deemed critically important fed to animals despite requests from KAW, members of Congress, and other advocacy organizations. The FDA released some further details on the data collected in 2009 to a

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4 Interagency Task Force on Antimicrobial Resistance. 2001. *A Public Health Action Plan To Combat Antimicrobial Resistance Part 1: Domestic Issues.* Available from: http://www.cdc.gov/drugresistance/actionplan/taskforce.html

5 World Health Organization. 2000. *Who Global Principles For The Containment Of Antimicrobial Resistance In Animals Intended For Food*. Available from: http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.4.pdf

6 OIE. 2012. *Monitoring Of The Quantities And Usage Patterns Of Antimicrobial Agents Used In Food Producing Animals.* In Terrestrial Animal Health Code. Available from: http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

7 FDA Science Advisory Board. 2007. *National Antimicrobial Resistance Monitoring System (NARMS) Program Review*. Available from http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4307b1_03_NARMS_Report.pdf.

8 P.L. 110-316.

9 *Antibiotic Resistance, Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals* (GAO-11-801 September 2011) (GAO Report) at 46. Available from: http://www.gao.gov/products/GAO-11-801.

member of Congress in 2011,[10] but has failed to release the same detailed information on the 2010 report despite repeated requests.

Given the FDA's longstanding failure to collect and make public this needed information, we are skeptical that this ANPR will result in Agency action. We are concerned that this ANPR instead will further delay needed action, and may be timed to reduce the likelihood that Congress will require that the FDA improve antimicrobial data use collection when ADUFA is reauthorized next year.

We urge FDA to release more detail on the data collected in 2009, 2010, and 2011, and to ask Congress to improve drug use data collection in its recommendation on ADUFA reauthorization.

Comments on specific questions posed by FDA:

A) Sponsors can provide separate sales and distribution data for each species.

In 2001, the FDA developed a proposed rule and associated guidance that required drug sponsors to provide "estimates of the quantity of antimicrobial activity used and the number of animals treated or exposed for each food animal production class listed on or inherent in the label by species."[11] The FDA should require sponsors to provide this information, as the FDA has already determined that this is within the agency's regulatory authority.

With increased integration, it is likely that a significant portion of sales are directly to the livestock industry contractors, who know the species for which drugs are intended. In addition, the Animal Health Institute (AHI) routinely publishes information on the amount of antibiotics used for growth promotion based on surveys of its members. This indicates that member companies have a level of detail on how their products are used that could be provided in the drug sales and distribution data.

B) FDA should compile and present summary information collected for 2009, 2010, and 2011 under Section 105 of ADUFA on medical importance, route of administration, and marketing statistics and deal with confidentiality concerns by aggregating data.

It is our understanding that Section 105 of ADUFA requires the FDA to make summaries available only by drug class, and limits independent reporting to classes with three or more independent sponsors. ADUFA does not put any other limitations on how FDA

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[10] Letter from Karen Meister FDA Supervisory Congressional Affairs Specialist to Representative Louis M. Slaughter, April 91, 2011. Available from: http://www.keepantibioticsworking.com/new/Library/UploadedFiles/FDA%20response%20to%20Slaughter%20data%20reques%20-%2004-2011.pdf

[11] Proposed Rule. *Status Reports of Distribution and Use Information for Antimicrobial Animal Drug Products Used in Food-Producing Animals, RIN: 0910-AC04. Draft Guidance for Industry #146 Status Reports of Distribution and Use Information for Antimicrobial Animal Drug Products Used in Food-Producing Animals, April 3, 2002.*

summarizes the data beyond a general recommendation that the reporting be consistent with "protecting both national security and confidential business information."[12]

While the legislation is silent on how classes that are not to be reported independently should be reported, the FDA summaries lump all antimicrobials that do not have at least three independent sponsors into a large umbrella group instead of creating smaller groups based on either relationships between drug classes or by medical importance. This decision has led to the combining of a critically important antibiotic class like the fluoroquinolones with a drug such as carbadox, which is not even used in human medicine.

Our recommendations to the FDA are as follows:

Break out drugs not independently reported by medical importance

We recommend that FDA should separate the data into smaller groups all with at least three distinct sponsors based on the ranking of medical importance as determined by the World Health Organization (WHO) ranking of critically important drugs.[13] We recommend that the WHO ranking be used because the FDA ranking is incomplete and has not been updated since 2003. Under this approach the drugs not independently reported would be placed into four separate groups: Critically important, Highly important, Important, and Not Important. Providing information on the quantities of drugs sold and distributed based on medical importance is needed because the risk from antimicrobial resistance is qualitatively higher for the more important drugs.[14] If confidentiality requirements make this type of grouping impossible, then FDA should at least separate drugs used in human medicine from those only used in food producing animals.

Provide information on dosage form/route of administration

In addition to breaking out data into classes based on medical importance, we recommend that FDA separately report on amounts of drugs administered by different routes such as in feed, by water, or by injection. The FDA states in its current summary reports that the summary table reflects "all approved uses of all dosage forms (e.g., injectable, oral, medicated feed) of the identified classes of actively marketed drugs in food-producing animals,"[15] and has previously provided information on route of administration pursuant to requests, indicating that FDA has the information available to it. This information is encompassed within the

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[12] P.L. 110-316.

[13] WHO list of Critically Important Antimicrobials. Available from: http://www.who.int/foodborne_disease/resistance/cia/en/

[14] FDA *Guidance for Industry #152 Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*. at 20. Available from: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

[15] FDA. 2009 SUMMARY REPORT on Antimicrobials Sold or Distributed for Use in Food- Producing Animals. Available from: http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf.

requirements of section 105 of ADUFA for drug manufacturers to report annual sales of antibiotics, including dosage form.[16] This information could be published in a separate table that would include data both from classes that are independently reported and those that are not. The table could be divided by the medical importance and the route of administration of the drug. For example, the table would show what amount of critically important antimicrobials are administered in feed.

As recognized by the FDA in its 2003 Guidance for Industry #152,[17] its 2012 Guidance for industry #209,[18] and the 2012 Draft Guidance for Industry #213,[19] the risk to the public health of drugs administered to whole herds or flocks via water or feed is substantially greater than the risk of drugs administered to animals individually, such as by injection. For this reason, the FDA should report antimicrobial use data by route.

Provide information on marketing status

Given that FDA has asked sponsors to change marketing status for antimicrobials in feed and water from over the counter (OTC) to prescription or veterinary feed directive[20] (VFD), we recommend that the FDA also report on amounts sold by marketing status, again broken out by medical importance. This step would provide an important tool to monitor whether or not FDA's voluntary plan is working.

Set a timeline for publicly reporting drug use data

While the drug companies must report their previous year's sales data by March 31, Section 5 of ADUFA gives no deadline for when the FDA must make its summaries public. The FDA made the 2009 summaries public in December 2010 and the 2010 summaries public in October 2011. The 2011 data were not yet public as of November 19, 2012.

In October 2009, the FDA indicated that there were only "29 animal drug manufacturers with 194 approved applications for antimicrobial drugs for food-producing animals for which the drugs are being actively marketed (active applications)."[21] While there is an expected delay in making the summaries public after the sales data is submitted, in light of the small number of firms that are

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16 P.L. 110-316; *see, e.g.,* 21 C.F.R. parts 520, 522, 524.

17 Ibid at 23.

18 FDA *Guidance for Industry #209 The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals.* Available from: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf

19 FDA. *Draft Guidance #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*. Available from: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf

20 Ibid.

21 74 Fed. Reg. 55046 (October 26, 2009) at 55047.

reporting data, it would be reasonable to expect a shorter delay between data collection and the public summary.

The FDA should publish summaries of drug data in a timely fashion to show whether its voluntary program is leading to a reduction in the amount of antibiotics used in food animals.

The FDA should also include in its regulation a date for public reporting of data no later than September 30.

We see no need for the FDA to wait for the completion of formal rulemaking to implement these recommendations on improved reporting on the data already collected by the Agency. As the FDA did release some of the data for 2009, there is no reason for the Agency to now reverse course.

C) The FDA should collect and publish antimicrobial drug sales data from manufacturers of medicated animal feeds. If it does not believe it has the authority to implement such a program, it should ask Congress to clarify that it has the legal authority.

We recommend that in addition to drug distribution data, the FDA also collect antimicrobial drug sales data from manufacturers of medicated animal feeds. Because feeds are specific to animal species and animal class, these data would contain much more detail than the drug distribution data required by Section 105 of ADUFA.

The GAO reports that animal feed mills currently "maintain records on antibiotics mixed into animal feed, including the amount of antibiotic used and the type of feed the antibiotic went into…[T]his information could be used to track antibiotic use by species."[22] We note that the FDA's current regulations require medicated feed manufacturers to maintain records on their sales of animal feed and to make them available to the FDA upon request.[23] The FDA told the GAO that "collecting use data from feed mills would require the development of a new reporting mechanism for these data."[24] Existing reporting mechanisms for sales data could be adapted for feed mills as well as drug manufacturers. Compiling, summarizing, and reporting this data would add vital information on food animal antibiotic use.

The *New York Times* recently reported that an official of the U.S. Poultry and Egg Association said the FDA has the authority to inspect and audit records on antibiotic use in animal feed; however, an FDA official said that the FDA does not have the authority to collect and publish such data.[25] We believe that FDA does have this authority. If the

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[22] GAO report at 14.
[23] 21 C.F.R. 225.110; 21 C.F.R. 225.202.
[24] GAO report at 15.
[25] New York Times ("Farm Use of Antibiotics Defies Scrutiny") (September 3, 2012 at D1). http://www.nytimes.com/2012/09/04/health/use-of-antibiotics-in-animals-raised-for-food-defies-scrutiny.html?_r=1

FDA believes it does not, then it would be prudent for the FDA to ask Congress to clarify that it does have such authority. A bipartisan letter on this issue sent August 13, 2012 and signed by 13 Senators (including the chair of the Appropriations subcommittee for Agriculture, Rural Development, Food and Drug Administration and Related Agencies) noted that they would welcome the opportunity to work with the FDA to provide additional authorities and resources.

In addition to using existing authorities to collect data from feed manufacturers, we recommend that the FDA include in changes to the Veterinary Feed Directive (VFD) a requirement that distributors of medicated feeds containing VFD drugs report to the FDA the amounts of antibiotics distributed in feed, along with information contained in the VFD on species, approximate number of animals treated, production class, and purpose of use. Drug distributors already are required to both maintain the records and to make them available on inspection.[26]

Conclusion:

The collection of veterinary drug use data is a key tool for the management of antimicrobial resistance. We strongly urge the FDA to release additional details on the data collected in 2009, 2010, and 2011 under ADUFA, and to ask Congress to improve drug use data collection in its recommendation on the impending ADUFA reauthorization. In addition, the Veterinary Feed Directive affords another method under FDA's existing authority to obtain and assess information. If you would like to speak with a representative from KAW or one of the undersigned organizations, please contact KAW Coalition Manager Lisa Isenhart at 773-525-4952 or lisenhart@keepantibioticsworking.com. We appreciate your consideration of our comments.

Sincerely,

Keep Antibiotics Working

Alliance for the Prudent Use of Antibiotics

Alliance of Nurses for Healthy Environments

American Academy of Pediatrics

American Academy of Pediatrics, District II (New York State)

American Academy of Pediatrics, Maine Chapter

American Academy of Pediatrics, New Jersey Chapter

American Society for Clinical Laboratory Science

Breast Cancer Action

Breast Cancer Fund

California Safe Schools

[26] 21 C.F.R 558.6 (e).

Center for Foodborne Illness Research & Prevention
Center for Food Safety
Center for Science in the Public Interest
Colorado Academy of Family Physicians
Delaware Public Health Association
Dignity Health
Food and Water Watch
Food Animal Concerns Trust
Healthcare Without Harm
The Humane Society of the United States
Humane Society Veterinary Medical Association
Institute for Agriculture and Trade Policy
Maine Medical Association
MRSA Survivors Network
National Association of Directors of Nursing Administration/Long Term Care, Inc.
Natural Resources Defense Council
New Jersey Pediatric Council of Research & Education
Ohio Nurses Association
Pennsylvania Pharmacists Association
Pennsylvania State Nurses Association
The Pew Charitable Trusts
Physicians for Social Responsibility
Physicians for Social Responsibility, San Francisco-Bay Area Chapter
San Francisco Medical Society
STOP Foodborne Illness
Union of Concerned Scientists
Washington Physicians for Social Responsibility