Comments of Consumers Union on
Food and Drug Administration (FDA) Advanced Notice of Proposed Rulemaking:
Antimicrobial Animal Drug Sales and Distribution Reporting
Docket No. FDA-2012-N-0447
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Consumers Union[1] (CU) welcomes the opportunity to comment on the U.S. Food and Drug Administration's (FDA) Advanced Notice of Proposed Rulemaking (ANPR) on antimicrobial animal drug sales and distribution reporting. We commend FDA for addressing the problem of overuse of antibiotics in food animals, which has created a serious global public health problem for both human and animals, and for the agency's attempts to reduce the injudicious use of antimicrobials in food-producing animals in order to help minimize antimicrobial resistance development. We also commend FDA for soliciting public comments on how to improve both data collection and public reporting of antimicrobial drug sales in order to better monitor the growing threat of antimicrobial resistance.

Last year, the U.S. Government Accountability Office (GAO) recommended that FDA collect "more detailed data on antibiotic use in food animals, including the species in which antibiotics are used and the purpose of their use" so as "To track the effectiveness of policies to curb antibiotic resistance, including FDA's voluntary strategy to reduce antibiotic use in food animals."[2] We strongly agree with GAO's recommendations and believe that FDA needs both to collect more data on antibiotic sales and use in livestock, poultry and aquaculture and report those data to the public so as to determine if the FDA's voluntary guidance approach, e.g. Guidelines for Industry (GFI) 209[3] and 213[4], is achieving its goals of reducing injudicious antimicrobial use and

[1] *Consumers Union is the public policy and advocacy division of Consumer Reports. Consumers Union works for telecommunications reform, health reform, food and product safety, financial reform, and other consumer issues. Consumer Reports is the world's largest independent product-testing organization. Using its more than 50 labs, auto test center, and survey research center, the nonprofit rates thousands of products and services annually. Founded in 1936, Consumer Reports has over 8 million subscribers to its magazine, website, and other publications.*

[2] Pg. 46 in Government Accountability Office (GAO). 2011. ANTIBIOTIC RESISTANCE: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals. GAO-11-801. At: http://www.gao.gov/new.items/d11801.pdf

[3] FDA. 2012. Guidance for Industry (GFI) #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. 26 pp. At: http://www.fda.gov/downloads/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216936.pdf

[4] FDA. 2012. Draft Guidance for Industry (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. 18 pp. At: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf

having the desired public health outcome of minimizing antimicrobial resistance development.

In general, CU believes that FDA should require companies to report sales and distribution data for each food-producing animal species for each antimicrobial active ingredient sold, and that FDA should release far more of the data collected as a result of Section 105 of the Animal Drug User Fee Amendments (ADUFA) of 2008. In addition, FDA should require annual reporting of data regarding antimicrobial drugs added to animal feed, as part of the Veterinary Feed Directive regulations, by veterinarians and feed mills in a standardized format and should aggregate those data into a publicly available registry that reports data for each separate food-producing animal species, by state and by month.

Specific comments on the questions posed by FDA in the ANPR are as follows:

Sales and Distribution Data by Species

Presently, Section 105 of ADUFA does not require sponsors of animal antimicrobials to disclose an estimate of the total amount of each approved active ingredient sold or distributed for each food producing species. Rather, if an antimicrobial is approved for multiple species, say poultry, swine and cattle, the manufacturer can simply report the total sales. If we do not have the antimicrobials sales data for each species, it is virtually impossible to determine what changes, if any, are happening within an animal species or between food animal sectors, e.g. tetracyclines use in poultry versus its use in swine versus its use in cattle versus its use in fish.

Without such information, we cannot accurately determine whether FDA's voluntary guidance approach, e.g. GFI 209 and Draft GFI 213, is reducing the use of antimicrobials in each species, thereby reducing injudicious use. Consequently, we wholeheartedly agree with FDA that "it should amend its regulations to require the submission of additional sales and distribution information including, for antimicrobial animal drug products that are approved and labeled for more than one food-producing animal species, an estimate of the amount of each active antimicrobial ingredient sold or distributed for use in each approved food-producing animal species."[5] This recommendation is long overdue as the Interagency Task Force on Antimicrobial Resistance's (ITFAR) 2001 Public Health Action Plan to Combat Antimicrobial Resistance lists as a "Top Priority Action Item," "Develop and implement procedures for monitoring antimicrobial use in human medicine, agriculture, veterinary medicine, and consumer products." One element of this action is to "Link agricultural drug-use data to species and usage patterns."[6] So, for more than ten years, the ITFAR, which FDA co-chairs, has called for gathering data on antimicrobial use at the food-producing animal species level. Thus, **FDA should**

[5] Pg. 44178 in 77 FR 44177, July 27, 2012. At: http://www.gpo.gov/fdsys/pkg/FR-2012-07-27/html/2012-18366.htm

[6] Pg. 16 in Interagency Task Force on Antimicrobial Resistance (ITFAR). 2001. Public Health Action Plan to Combat Antimicrobial Resistance. At: http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf

amend their ADUFA rules to require sponsors of an antimicrobial drug to report separately sales and distribution data for each food-producing animal species for each antimicrobial active ingredient.

FDA's Annual Summary Report

Section 105 of ADUFA requires FDA to make annual summaries of the reported information available. At present, FDA only makes available total antimicrobial sales each year by drug class and only those antimicrobial classes with three or more distinct sponsors of approved actively marketed animal drug products are independently reported. These publicly available annual summary reports contain too little information, and would be most helpful if they contained additional data. FDA should add the following five elements (three of which the industry already reports) to the publicly-available annual summary to dramatically increase its utility in analyzing antimicrobial usage and resistance trends:

1. *Animal* species: FDA should report antimicrobial sales and distribution data by **animal species** in total and for each antimicrobial class. Presently, the summary data for antimicrobial drugs approved in food-producing animals only gives annual aggregate data for each antimicrobial class. For antimicrobial active ingredients that are approved for use in multiple species, this means data from non-food producing animals (e.g. dogs, cats, horses, etc.) are lumped with data from food-producing animals (e.g. cattle, pigs, chicken, turkeys, etc.). Indeed, of the nine antimicrobial classes (including NIRs [not independently reported]) for which data are reported domestically, only two (aminoglycosides and ionophores) include data solely from food-producing animals. Thus, using the 2010 data on antimicrobials sold or distributed within the United States[7], this means that roughly only 30.4% of the antimicrobials, by weight, were used exclusively on food producing animals; for the other 69.6%, we do not know how much was used on food producing animals versus nonfood producing-animals. Further, by not reporting separately the sales and distribution data for each food-producing animal species, we not only cannot know how much was used on food-producing animals, we also have no way of knowing what changes in antimicrobial use are happening both within a food-producing species and between different animal sectors, e.g. cattle versus poultry versus swine versus fish; such data are crucial in determining if FDA's voluntary guidance on judicious use is having any impact. Ideally, **FDA should report data for each separate food-producing animal species so as to accurately be able to determine how antibiotic usage is changing by species**. At the least, FDA could report the data for each of the major use food animal species, e.g. cattle, pigs, chickens and turkey.

2. *Dosage Forms*: FDA should report the **dosage form** (e.g. injectable, oral, medicated feed) of antimicrobials **both in total and as a class**. Data on dosage

[7] FDA. 2011. 2010 SUMMARY REPORT on Antimicrobials Sold or Distributed for Use in Food-Producing Animals. 4 pp. At: http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM277657.pdf

forms are already required to be reported to the FDA under Section 105 of ADUFA, but are not made available in the annual summary reports. By reporting the dosage form in the annual summary reports, consumers can get a better idea of the identity and quantity of antibiotics given to individual animals (e.g. via injection) versus given to groups of animals (e.g. via drinking water or via medicated feed). Such reporting would fulfill one of Top Priority Action Items from ITFAR's 2001 Public Health Action Plan to Combat Antimicrobial Resistance, e.g. "Link agricultural drug-use data to species and usage patterns."[8]

A 2011 study by scientists at John Hopkins University found that use of medicated feeds "can result in a failure to resolve animal diseases and in the development of antimicrobial-resistant microorganisms"[9]. According to a letter sent from the FDA to Representative Louise Slaughter, some 74% of the antimicrobials sold in the US in 2009 were distributed via medicated feed, while only 3% were sold via injection.[10] The large majority of antimicrobials sold or distributed in the US is administered via a method—medicated feed—that has been linked to the development of antimicrobial-resistant organisms. The most accurate method of administering antimicrobials to food animals—injection—would minimize the chance of development of antimicrobial-resistant organisms, but was only used on a tiny fraction of the food-producing animals, according to FDA's letter to Representative Slaughter. Without the information requested by Mrs. Slaughter, we could not begin to understand the reasons behind growing antimicrobial resistance, such as medicated feed. But rather than relying on requests for information from Representatives, **FDA should annually report dosage forms for antimicrobials both in total and by drug class for each food-producing animal species.** Such reporting would help us to understand how best to reduce injudicious use of antimicrobials and to combat the public health problems posed by growing resistance.

3. *Data by Month*: FDA should report antimicrobial sales and distribution **by month**. Data on monthly sales and distribution are already required to be reported to the FDA under Section 105 of ADUFA but are not made available in the annual summary reports. Reporting antimicrobial sales and distribution by month in these summary reports can help provide useful data on use by season which may have an impact on antibiotic resistance. For example, if the sales and distribution for a given antimicrobial class and given food-producing animal species shows dramatic spikes in a given month, that could give some indication of the kind of problems encountered in production systems for that animal species. Thus, **FDA should include in its annual summary report, the**

[8] Pg. 16 in ITFAR. 2001. Op cit.
[9] Pg. 279 in Love DC, Davis MF, Bassett A, Gunther A and KE Nachman. 2011. Dose imprecision and resistance: free-choice medicated feeds in industrial food animal production in the United States. *Environmental Health Perspectives*, 119(3): 279-283. At: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059987/pdf/ehp-119-279.pdf
[10] http://www.louise.house.gov/images/stories/FDA_Response_to_Rep._Slaughter.pdf

antimicrobial sales and distribution both in total and by drug class for each food-producing animal species, by month.

4. *Data by State*: FDA should report antimicrobial sales and distribution **by state**. Another "Top Priority Action Item" from ITFAR's 2001 Public Health Action Plan to Combat Antimicrobial Resistance is to "Develop and implement procedures for monitoring antimicrobial use in human medicine, agriculture, veterinary medicine, and consumer products." One element of this action item is to "Assess potential effects of geographic variations in drug use on the incidence and prevalence of antimicrobial resistance."[11] In order to assess such geographic variations, FDA should provide the antimicrobial sales and distribution for each state. Such data, when separated by each food-producing animal species, could also indicate if there are regional differences in the amount of antimicrobials being used to produce a particular food-producing animal species. If a particular state uses far more antimicrobials to produce the same amount of food-producing animal species compared to another state, this could indicate stronger selection pressure for antimicrobial resistance or greater environmental release. In addition, such data could help us better understand the scope of the environmental release of antimicrobial resistance genes. A study of the South Platte River in Colorado released last month found that antibiotic resistance genes (coding for resistance to sulfonamides) were 10,000 times higher in river sediments downstream from larger feedlots (ones with 10,000 cattle) compared to river sediment upstream from such feedlots.[12] This study also found that these same antibiotic resistance genes were only 1,000 times higher from sewage treatment plants that discharge ten million gallons of effluent per day, compared to pristine sediments. Thus, the higher the quantities of antimicrobials used within a state in such large industrial food animal production facilities, the greater the potential environmental release of antibiotic resistance genes, which could be important in determining prevalence of antimicrobial resistance. Consequently, to better monitor antimicrobial use, **FDA should require reporting of antimicrobial sales and distribution both in total and by drug class for each food-producing animal species on a state-by-state basis**.

5. *Drug Classes Used in Human Medicine Not Individually Reported*: FDA should report **both in aggregate form and** separately (from those not important in human medicine) those antimicrobials that *are* important in human medicine, but which are not individually reported. Section 105 ADUFA does not allow FDA to independently report antimicrobial drug classes that only have one or two distinct sponsors, so as to protect confidential business information (CBI). For the 2010 Summary report put out by FDA,[13] there were 9 classes of antimicrobial drugs that were sold or distributed in the US that were Not Independently Reported

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[11] IBID

[12] Pruden A, Arabi M and HN Storteboom. 2012. Correlation between upstream human activities and riverine antibiotic resistance genes. *Environmental Science & Technology*, dx.doi.org/10.1021/es302657r At: http://pubs.acs.org/doi/abs/10.1021/es302657r

[13] FDA. 2011. Op cit.

(NIR): aminocoumarins, amphenicols, diaminopyrimidiens, flouroquinolones, glycolipids, pleuromutilins, polypeptides, quinoxalines, and streptogramins. These NIRs represented 11% of the antimicrobials sold or distributed nationally and 95% of the antimicrobials exported. For the domestic data, three of these antimicrobial classes—flouroquinolones, polypeptides, and streptogramins—contain antimicrobial drugs that are either critically important or highly important in human medicine, according to FDA's GFI #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern."[14] FDA could separate the NIR and NIRE (Not Independently Reported Export) categories into those antimicrobial drugs that are important, highly important, or critically important (according to FDA's GFI #152), and those classes that are not important in human medicine and report these two categories—important in human medicine and not important in human medicine—separately. For the domestic data, this would mean aggregating the data for flouroquinolones, polypeptides, and streptogramins and reporting it separately from the other six antimicrobial classes in NIR category. By doing this, the public could get valuable information on the use and distribution of these important antimicrobials, without compromising CBI and running afoul of Section 105 of ADUFA. Thus, **FDA should divide the NIR and NIRE drug classes into two sub-classes—those that are important in human medicine and those that are not important in human medicine—and then require reporting of antimicrobial sales and distribution, both in total and for each food-producing animal species, for each sub-class**.

Alternative Methods for Obtaining Antimicrobial Use Data

In addition to the reporting requirements of Section 105 of ADUFA, there are a few alternative ways that FDA could obtain antimicrobial use data. One such alternative method that is within FDA's existing authority involves the Veterinary Feed Directive (VFD) regulation. A VFD drug is an approved animal drug for use in or on animal feed, and must be used under the professional supervision of a licensed veterinarian.[15] All VFD drugs can only be manufactured by a feed mill that has a medicated feed mill license, which has to be obtained from the FDA. The VFD regulations require that both the veterinarian and the feed mills retain copies of the VFD which includes, among other things, the name of the animal drug, the animal species, the number of animals to be treated/fed the medicated feed, the location of the animals, the date of treatment, and the indication for which the VFD was issued. Earlier this year, FDA proposed changes to the

[14] See Appendix A in FDA. 2003. 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: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf

[15] FDA. 2009. Guidance for Industry #120. Veterinary Feed Directive Regulation Questions and Answers. 11 pp. At: http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052660.pdf

VFD[16] that would allow for electronic requests and record keeping, and which would transition new animal drug products containing medically-important antimicrobial drugs from an over-the-counter status to a status that requires veterinary oversight. These proposed changes, which CU supports, would increase the number of drugs and feed mills affected by VFDs and would give FDA significantly more data on intended drug usage. Since data from 2009 show that 74% of all antimicrobials used or distributed in the US were medicated feeds[17], requiring the reporting of such data could be crucial in enabling a meaningful analysis of those factors related to the development and spread of antimicrobial resistance as a result of use of antimicrobials of importance in human medicine. Thus, **FDA should enact its proposed changes to VFDs, and require annual reporting of VFD data by veterinarians and feed mills in a standardized format. FDA should also aggregate those data into a publicly available registry that reports data for each separate food-producing animal species, by state and by month.**

Second, since the VFD regulations cover some three-quarters of all antimicrobials sold or distributed in the US, FDA could ask for the prescribing data from veterinarians for those antimicrobial drug dosage forms not covered by VFDs, e.g. injectable antimicrobial drugs and antimicrobials administered to a food-producing animal via drinking water, on each food-producing animal species. Although FDA does not currently have the statutory authority to require such data to be turned over, they could request veterinarians to voluntarily submit such data. In Denmark, all veterinarians must submit data on prescriptions for all antimicrobial drugs on a per farm basis.

Third, FDA could ask producer organization for any data they have on usage and patterns of usage from their members. For example the National Pork Producers Council has a Pork Quality Assurance Plus (PQA Plus) program that requires producers to have a veterinarian/client/patient relationship, identify and track all treated animals and to maintain medication and treatment records.[18] Although FDA does not have the statutory authority to require such data to be turned over, they could request producer organization to voluntarily submit such data.

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[16] FDA. 2012. 21 CFR Part 558 [Docket No. FDA-2010-N-0155] Veterinary Feed Directive; Draft Text for Proposed Regulation. 77 *Federal Register*, No. 72, Friday, April 13, 2012. At: http://www.gpo.gov/fdsys/pkg/FR-2012-04-13/pdf/2012-8844.pdf

[17] http://www.louise.house.gov/images/stories/FDA_Response_to_Rep._Slaughter.pdf

[18] See: http://www.nppc.org/issues/animal-health-safety/pork-quality-assurance-plus-pqa-plus/