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

By Hand

Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152

A. Action Requested

On behalf of Environmental Defense, the American Academy of Pediatrics, the American Public Health Association, and the Union of Concerned Scientists (hereinafter referred to as the Petitioners),[1] the undersigned submits this petition[2] under section 512(e) of the Federal Food, Drug, and Cosmetic Act (FDCA) to request the Commissioner to withdraw approvals for herdwide/flockwide uses of the below-listed antibiotics[3] in chicken, swine, and beef cattle for purposes of growth promotion (including weight gain and feed efficiency) and disease prevention and control (except for non-routine use where a bacterial infection has been diagnosed within a herd or flock):

- Penicillins (natural penicillins, penase resistant penicillins,[4] antipseudomonal penicillins, and aminopenicillins)
- Tetracyclines
- Aminoglycosides
- Streptogramins
- Macrolides
- Lincomycin
- Sulfonamides

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[1] See Appendix 1 for descriptions of the Petitioners.
[2] This petition follows the format required by FDA's regulations governing Citizen Petitions. See 21 C.F.R. 10.30. Available at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=10.30 (accessed Apr. 5, 2005).
[3] While antibiotics are technically a subset of antimicrobials, this petition uses the term "antibiotic" as synonymous with the more technical term "antimicrobial" because the latter is not used in general parlance.
[4] Also referred to as penicillinase-resistant penicillins.

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Specifically, we request that the Commissioner promptly initiate and conclude proceedings to rescind or amend existing approvals covering the drug uses specified in the Addendum to this Petition.[5]

The requested actions are consistent with the criteria set forth in Guidance #152, issued by the Food and Drug Administration (FDA) on October 23, 2003,[6] and with the positions of numerous public health and medical experts. As the first line of the Guidance notes, that document lays out a "recommended approach for assessing the safety" of agricultural antibiotics with regard to antibiotic resistance.

The drugs covered by this Petition meet both of two criteria. First, they are designated (individually or as a member of a drug class) as a "critically important" or "highly important" antibiotic under the Guidance. Second, they are approved for use in chicken, swine, or beef cattle for growth promotion (including weight gain and feed efficiency), disease prevention, or disease control. However, Petitioners do not seek withdrawal of disease prevention or disease control uses where a drug is administered to individual animals, or to select groups or pens of animals,[7] or where a drug is administered in response to a diagnosed outbreak of bacterial disease within a building, house, or feedlot.[8] Insofar as withdrawal of existing approvals would bar uses of these prevention/control uses, Petitioners request that FDA instead amend the approvals to permit *only* disease prevention/control that involves administration to an individual animal, or to select groups or pens of animals, or in response to a diagnosed outbreak of bacterial disease within a building, house, or feedlot. **It is important to note that this Petition does *not* cover any uses of any drugs for disease treatment.**

While the Guidance would encompass additional use restrictions beyond those covered in this Petition, we believe that the Petition covers the most clear-cut examples of inappropriate use on which FDA should take immediate action. This is because the uses covered by the Petition account for the greatest volumes of uses of medically important antibiotics, and because elimination of these uses can most readily be accomplished. Indeed, other nations – notably Denmark, the world's largest exporter of pork – have already done so, and high-volume meat purchasers in the U.S. are increasingly seeking meats produced without routine use of antibiotics (see next section below).

Though not a basis for this petition *per se,* it is noteworthy that FDA has never determined that the existing herdwide/flockwide uses covered by this Petition meet modern scientific standards for safety with regard to antibiotic resistance. These uses

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[5] For some of the drug uses covered by the petition, FDA initiated proceedings in the mid-1970s, but to date has not taken final action with regard to those proceedings and they remain pending. See Appendix 3 and materials cited therein.

[6] Guidance for Industry #152, Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs with regard to their Microbiological Effects on Bacteria of Human Health Concern, Oct. 23, 2003. Available at www.fda.gov/cvm/guidance/fguide152.pdf (accessed Apr. 5, 2005).

[7] The phrase "select groups or pens of animals" is taken from page 23, Table 7 of the Guidance.

[8] The phrase "within a building, house [or] feedlot" is taken from page 23 of the Guidance.

were initially approved decades ago. While FDA requested supplemental data in the 1970s relating to antibiotic resistance, those data were generated using test methods so seriously flawed that even the trade association for the animal-drug industry has recently acknowledged that they "are not predictive."[9] As a senior FDA scientist has observed, "These studies, as designed, are 30 years old. Science has moved on."[10] See Appendix 2.

Moreover, FDA has itself acknowledged that some of the uses covered by this Petition are inconsistent with this Guidance. In May 2004, FDA sent letters to four producers of penicillin feed additives approved for growth-promoting uses (copies of the letters, which were obtained under the Freedom of Information Act, are contained in Appendix 3). Each letter stated in part:

> "The administrative record does not contain sufficient information to alleviate [FDA's] concern about the use of these products and their possible role in the emergence and dissemination of antimicrobial resistance. ... The outcome of the qualitative risk assessment conducted [by FDA] according to Guidance #152 is that the product is considered Category 1 [i.e., high risk]. "

The agency concluded by noting that growth promotion and related uses "are not considered appropriate for Category 1 or 2 products under Guidance #152." Unfortunately, in the ten months since these letters were sent, the manufacturers of these products have failed to comply with FDA's implicit request to voluntarily remove these substances from the market.

B. Statement of Grounds

1. Background: The Emerging Medical Crisis of Antibiotic Resistance and the Agricultural Use of Antibiotics

A number of prominent health-focused institutions have flagged antibiotic resistance as a serious problem for human medicine. The Centers for Disease Control has identified antibiotic resistance as one of its "top concerns."[11] A federal interagency task force including representatives from FDA recently noted that antibiotic resistance is "a growing menace to all people" and that, absent effective action, treatments for common infections "will become increasingly limited and expensive – and, in some cases,

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[9] Animal Health Institute, Alexander S. Mathews, President & CEO. Comments to FDA Docket No. 98D-0969, "FDA Workshop on Pre-Approval Studies in Antimicrobial Resistance and Pathogen Load," May 3, 2000. Available at www.fda.gov/cvm/Documents/VMACAHIComments1..pdf (accessed Apr. 5, 2005).

[10] Remarks of Jean Cooper, FDA, "'558.15' studies: A historical perspective," at FDA public meeting "Pre-Approval Studies in Antimicrobial Resistance and Pathogen Load." (Feb. 22, 2000) (p. 121). Meeting transcript available at www.fda.gov/cvm/Documents/CVM-PSES222.doc (accessed Apr. 5, 2005).

[11] Centers for Disease Control (CDC). Background on Antibiotic Resistance. Atlanta, GA. Available at www.cdc.gov/drugresistance/community (accessed Apr. 5, 2005).

nonexistent."[12] The Infectious Disease Society of America warns that the pipeline of new drugs to combat bacterial diseases is "drying up" even as bacteria are becoming increasingly resistant to existing antibiotics.[13] The new-drug drought reflects in part the fact that it is far more profitable for pharmaceutical companies to develop drugs to treat chronic conditions because a patient must take those drugs for years. By contrast, in most instances a patient need take antibiotics only for a week or so.

In 1998, the National Academy of Sciences stated that antibiotic-resistant bacteria "generate a minimum of $4 billion to $5 billion in costs to U.S. society and individuals yearly."[14] Patients infected with drug-resistant organisms "are more likely to have longer hospital stays and require treatment with second- or third-choice drugs that may be less effective, more toxic, and/or more expensive."[15]

In addition, numerous expert organizations have recognized that, along with medical overuse of antibiotics, agricultural overuse of antibiotics contributes to the development and spread of resistant bacteria, imperiling human health:

- National Academy of Science's Institute of Medicine: "Clearly, a decrease in the inappropriate use of antimicrobials in human medicine alone is not enough. Substantial efforts must be made to decrease inappropriate overuse of antimicrobials in animals and agriculture as well."[16]
- World Health Organization: "There is clear evidence of the human health consequences [from agricultural use of antibiotics, including] infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections."[17]
- Alliance for the Prudent Use of Antibiotics: "the elimination of nontherapeutic use of antimicrobials in food animals and in agriculture will lower the burden of antimicrobial resistance in the environment with consequent benefits to human and animal health."[18]

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[12] Interagency Task Force on Antimicrobial Resistance (undated). A Public Health Action Plan to Combat Antimicrobial Resistance, p. 9. Available at www.cdc.gov/drugresistance/actionplan/aractionplan.pdf (accessed Apr. 5, 2005).

[13] Infectious Diseases Society of America (2004). Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews, p. 3. www.idsociety.org/pa/IDSA_Paper4_final_web.pdf (accessed Apr. 5, 2005).

[14] National Academy of Sciences Institute of Medicine (1998). Antimicrobial Resistance: Issues and Options. Washington, DC: National Academies Press, p. 1. Available at http://www.nap.edu/openbook/0309060842/html/1.html#pagetop (accessed Apr. 5, 2005).

[15] Centers for Disease Control, Campaign to Prevent Antimicrobial Resistance in Healthcare Settings: Why a Campaign? www.cdc.gov/drugresistance/healthcare/problem.htm (accessed Apr. 5, 2005).

[16] Institute of Medicine, Board on Global Health (2003). Microbial Threats to Health: Emergence, Detection, and Response. National Academy of Sciences Press, Washington, DC. Available at http://books.nap.edu/books/030908864X/html/207.html#pagetop (accessed Apr. 5, 2005).

[17] Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance (2003), p. 1. www.who.int/foodsafety/publications/micro/en/report.pdf (accessed Apr. 5, 2005).

[18] APUA, The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences. *Clinical Infectious Diseases*, Vol. 34 Supp 3, p. S75 (footnote omitted). Available at www.journals.uchicago.edu/CID/journal/contents/v34nS3.html (accessed Apr. 5, 2005).

In addition, the Department of Health and Human Services has itself noted that "there is a preponderance of evidence that the use of antimicrobials in food-producing animals has adverse human consequences."[19]

Unsurprisingly, the U.S. trade association for producers of agricultural antibiotics, the Animal Health Institute (AHI), opposes restrictions on use of agricultural antibiotics, as do certain meat producers and the American Veterinary Medical Association. As the U.S. General Accounting Office (subsequently renamed the Government Accountability Office) noted in its recent report on agricultural antibiotics, "Many studies have found that the use of antibiotics in animals poses significant risks for human health, but a small number of studies contend that the health risks of the transference are minimal."[20] The latter include a recent review article by Phillips *et al.*[21] In the article, the authors state that they "were initially convened as an advisory board" by AHI and that "We are grateful to AHI who kindly agreed to cover the costs of the preparation of this review: circulation of drafts, acquisition and circulation of references, and production of fair copy based on the drafts."

The Phillips *et al.* article has been sharply criticized by, among others, senior scientific officials at both FDA and CDC. For example, the Deputy Director of FDA's Center for Veterinary Medicine noted that the Phillips article "contains several factual errors" and further noted that their assessment "diverges from the majority of the peer-reviewed scientific literature on the subject, casting doubt on how objectively the authors reviewed the published data. The credibility of the authors' assessment is further strained by frequent improper citation of the published literature."[22] Similarly, CDC scientists noted that Phillips *et al.* had "incorrectly linked these [CDC] studies to statements that do not summarize the conclusions of the authors."[23] Other scientists characterized the article as

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[19] Comments from the Department of Health and Human Services, Appendix VII (p.89) *in* U.S. General Accounting Office (2004), *Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals.* GAO-04-490. Available at www.gao.gov/new.items/d04490.pdf (accessed Apr. 5, 2005).

[20] U.S. General Accounting Office (2004). *"Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals"*, report no. 04-490, unnumbered first page. Available at www.gao.gov/new.items/d04490.pdf (accessed Apr. 5, 2005).

[21] I. Phillips, M. Casewell, T. Cox, B. De Groot, C. Friis, R. Jones, C. Nightingale, R. Preston, and J. Waddell (2004). "Does the Use of Antibiotics in Food Animals Pose a Risk to Human Health? A Critical Review of Published Data," *Journal of Antimicrobial Chemotherapy*, 53: 28-52.

[22] L. Tollefson (2004). "Factual errors in review article," *Journal of Antimicrobial Chemotherapy* 54: 271-271 (footnote omitted). Dr. Tollefson, a veterinarian, is the Deputy Director of FDA's Center for Veterinary Medicine, and holds the rank of Assistant Surgeon General (Rear Admiral). See www.fda.gov/cvm/CVM_Updates/tollpromo.htm (accessed Apr. 5, 2005).

[23] T.M. Chiller, T. Barrett and F. J. Angulo (2004). "CDC studies incorrectly summarized in 'critical review'," *Journal of Antimicrobial Chemotherapy*, 54: 275-276. Dr. Chiller is Chief of the NARMS (National Antimicrobial Resistance Monitoring Systems) Unit at CDC. Dr. Barrett is Chief of CDC's FoodNet and NARMS Laboratory. Dr. Angulo, who holds both a DMV and an Ph.D. in epidemiology, is Chief of CDC's FoodNet and NARMS Unit. See www.cdc.gov/narms/staff.htm (accessed Apr. 5, 2005).

"fraught with inaccurate and misleading citations and other errors,"[24] and pointed to instances of "misquoting and misinterpreting scientific results."[25] Consistent with its usual practice, GAO requested comments on a prior draft of the report from relevant federal agencies, including the Department of Health and Human Services; HHS's comments included the statement that "We believe GAO should note in its report that the article they cite [i.e., Phillips *et al.*] was written by an advisory group to the Animal Health Institute."[26]

In addition, HHS's comments on the GAO report summarize recent scientific literature indicating that the very bacteria that are resistant may also be more virulent:[27] "In a prospective CDC study of 758 salmonellosis cases, patients with resistant infections were significantly more likely [to] be hospitalized than were those with susceptible infections, even after accounting for underlying illness and prior antimicrobial exposure using multivariate techniques." In addition, the comments described studies showing substantially increased mortality in the two years following infection with resistant S. Typhimurium compared to susceptible S. Typhimurium, and similar results for resistant versus susceptible *Campylobacter* infections.

Recent research also indicates that resistant foodborne bacteria are associated with ailments not traditionally regarded as foodborne illnesses, namely urinary tract infections (UTIs). As the authors of the most recent study noted, "The possibility that human drug-resistant UTI could be a foodborne illness has serious public health implications."[28]

2. *The Development of Guidance #152*

As detailed in Part III of this Petition, the actions requested herein are consistent with FDA's Guidance #152. As FDA noted in releasing the Guidance, that document "outlines a comprehensive evidence-based approach to preventing antimicrobial resistance that may result from the use of antimicrobial drugs in animals."[29] The Guidance reflects

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[24] B.E. Karp and J.Engberg (2004). "Comment on: Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data," *Journal of Antimicrobial Chemotherapy*, 54(1): 273-274. Dr. Karp is a Veterinary Medical Officer in the Division of Epidemiology at FDA's Center for Veterinary Medicine. See http://www.fda.gov/cvm/cvmlist4.html (accessed Apr. 5, 2005).

[25] V.F. Jensen, J. Neimann, A.M. Hammerum, K. Mølbak, and H.C. Wegener (2004). "Does the use of antibiotics in food animals pose a risk to human health? An unbiased review?," *Journal of Antimicrobial Chemotherapy*, 54(1): 274-275. The authors are scientists with the Danish Institute for Food and Veterinary Research and the Statens Serum Institut.

[26] GAO Report no. 04-490, p. 89, www.gao.gov/new.items/d04490.pdf.

[27] Ibid., p. 90.

[28] M. Ramchandani, A.R. Manges, C. DebRoy, S.P. Smith, J.R. Johnson, and L.W. Riley (2005). "Possible Animal Origin of Human-Associated, Multidrug-Resistant, Uropathogenic Escherichia coli." Clinical Infectious Diseases 40: 251-257. Available at www.journals.uchicago.edu/CID/journal/issues/v40n2/34442/brief/34442.abstract.html (accessed Apr. 5, 2005).

[29] FDA, "FDA Issues Guidance on Evaluating the Safety of Antimicrobial New Animal Drugs to Help Prevent Creating New Resistant Bacteria" (press release), Oct. 23, 2003. Available at www.fda.gov/bbs/topics/NEWS/2003/NEW00964.html (accessed Apr. 5, 2005).

the results of a careful deliberative process lasting nearly five years. During that period, FDA held numerous public meetings, proposed two earlier approaches for evaluating agricultural antibiotics (the "Framework"[30] document and the "Thresholds"[31] document), and developed a prior draft of the Guidance.[32] In addition, FDA held multiple public meetings and also solicited (and received) public comment. The final Guidance is thus the result of a procedure that has involved extensive public as well as agency involvement over several years.

Issuance of the final Guidance was hailed both by industry and advocates. For example, a press release issued by the Animal Health Institute was headlined "Industry Welcomes New FDA Guidance on Antibiotics," and noted that "This is the culmination of a process that has dragged on nearly five years."[33] AHI further lauded the guidance as a "risk-based approach" that "will allow FDA to make sound management decisions." Similarly, Keep Antibiotics Working's press release "applauded" release of the Guidance (though noting with dismay the absence of a schedule for taking action with regard to already-approved antibiotics).[34]

3. Legal Standard for Withdrawal of Animal Drugs

a. The Standards of FDCA Section 512 and Guidance #152

Animal drugs can only be marketed if approved by FDA under section 512 of the Food Drug and Cosmetics Act; FDA's mechanism for granting such approvals is termed a "new animal drug application," or NADA. Somewhat confusingly, all animal drugs now on the market are thus termed "new animal drugs," even though many have been on the market for decades.

Section 512 specifies that a NADA must be denied if the Secretary of Health and Human Services finds that available data show that a drug is "**unsafe**" for use under the proposed use conditions or the data "**do not show that such drug is safe**" under such

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[30] FDA Docket No. 98D-1146 - Discussion Paper: "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals." (64 Fed. Reg. 887, Jan. 6, 1999). Available at www.fda.gov/cvm/VMAC/antimi18.html (accessed Apr. 5, 2005).

[31] "An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-Producing Animals" (Dec. 19, 2000). Available at www.fda.gov/cvm/Documents/threshold21.pdf (accessed Apr. 5, 2005).

[32] FDA, "Draft Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern," 67 Fed. Reg. 58058-58060 (Sept. 13, 2002). Available at www.fda.gov/OHRMS/DOCKETS/98fr/98d-1146-gdl0001.doc (accessed Apr. 5, 2005).

[33] Animal Health Institute Press Release, Oct. 23, 2003. Available at www.ahi.org/mediaCenter/documents/Guidance152.pdf (accessed Apr. 5, 2005).

[34] Keep Antibiotics Working Press Release, Oct. 23, 2003. Available at www.iatp.org/antibiotics/library/uploadedfiles/KAW_Applauds_FDA_Issuance_of_Final_Guidance_Bu.pdf (accessed Apr. 5, 2005).