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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

FDA Docket Number 2005P-0139/CP 1
(Filed by FDA 04/08/05)

*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 petition² 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 antibiotics³ 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

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/cfcr/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.

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).

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.

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 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

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/VMACAHICComments1..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).

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, 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

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).

antimicrobial resistance in the environment with consequent benefits to human and animal health.”¹⁸

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

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).

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).

summarize the conclusions of the authors.”²³ Other scientists characterized the article as “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*

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).

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).

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 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

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).

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).

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 conditions;³⁵ the NADA must also be denied if the Secretary finds that there is “insufficient information to determine whether such drug is safe for use under such conditions.”³⁶ Section 512 also lays out the conditions under which a previously granted NADA is to be withdrawn, i.e., if the Secretary finds that the drug is “**unsafe**” for use under the approved conditions, or if evidence “**shows that such drug is not shown to be safe**” for such use.³⁷

Thus, the legal and public health standard for granting and withdrawing NADA approvals are substantively identical, i.e., if a use is either shown to be “unsafe” or is “not shown to be safe.”

In Guidance #152, FDA states that it considers an agricultural antibiotic to be “safe” if the agency “concludes that there is reasonable certainty of no harm to human health from the proposed use of the drug in food-producing animals.” While Guidance #152 was initially directed at drug producers seeking approval to market additional drugs, the Guidance’s criteria apply equally to existing NADAs for drugs now on the market, given that there is no scientific or legal distinction between standards for approval and standards for withdrawal.

³⁵ FDCA § 512(d)(1)(A) & (B), 21 U.S.C. § 360b(d).

³⁶ FDCA § 512(d)(1)(D), 21 U.S.C. § 360b(d).

³⁷ FDCA § 512(e), 21 U.S.C. § 360b(e) (emphasis added). Implementing regulations parallel the language of the statute. 21 C.F.R. § 514.115(b). The relevant text of section 512(e) reads as follows:

- (1) The Secretary shall, after due notice and opportunity for a hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) of this section with respect to any new animal drug if the Secretary finds—
 - (A) that experience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved ...;
 - (B) that new evidence not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved

....

As a practical matter, in withdrawing a drug FDA must “provide a reasonable basis from which serious questions about the ultimate safety [of a drug] may be inferred.”³⁸ Such questions “can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect.”³⁹ Once an initial showing of “serious questions” is made, the burden shifts to the drug manufacturer to establish that the use in question is “shown to be safe.”⁴⁰

b. The Criteria in Guidance #152 Are Applicable to Existing Approvals for Agricultural Antibiotics Now on the Market

As FDA noted in its Press Release on Guidance #152, the Guidance is “the first [document] that addresses, in a comprehensive manner, the issue of the use of antimicrobials in food producing animals as a contributing factor to the development of antimicrobial resistance.”⁴¹ Although the Guidance on its face applies only to *future* applications for approval of antimicrobials rather than to drugs already on the market, the 2003 Annual Report for FDA's Center for Veterinary Medicine states that the Guidance's “principles will also be applied in determining whether to remove approved products from the market.”⁴² In addition, FDA's Federal Register notice for the Guidance states “The guidance represents the agency's current thinking about the safety of [agricultural-animal] drugs, with regard to their microbiological effects on bacteria of human health concern.”⁴³

As demonstrated in the following section of this Petition, applying the Guidance's criteria to the petitioned drug uses indicates that those uses are inconsistent with the Guidance. As a result, “serious questions” clearly exist with regard to the safety of these uses. Accordingly, FDA should promptly initiate and conclude the process of withdrawing those uses.⁴⁴

³⁸ Proposal to Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry, docket no. 00N-1571. Initial Decision of March 16, 2004, at p. 5. Available at www.fda.gov/ohrms/dockets/dailys/04/mar04/031604/00n-1571-idf0001-vol389.pdf (accessed Apr. 5, 2005). Fluoroquinolones are **not** approved for use as feed additives, and this Petition **does not** cover use of fluoroquinolones.

³⁹ *Ibid.*, p. 5 (embedded quotation marks and citations omitted).

⁴⁰ *Ibid.*, p. 7.

⁴¹ 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).

⁴² U.S. Department of Health and Human Services, Food and Drug Administration, Center for Veterinary Medicine. Annual Report – Fiscal Year 2003 (October 1, 2002 - September 30, 2003), p. 20. Available at www.fda.gov/cvm/Documents/CVMFY03AnnRpt.pdf (accessed Apr. 5, 2005).

⁴³ 68 Fed. Reg. 61221 (Oct. 27, 2003). Available at www.fda.gov/OHRMS/DOCKETS/98fr/03-27113.pdf (accessed Apr. 5, 2005).

⁴⁴ As noted above, withdrawals for certain uses of some drugs were initiated in the 1970s and remain pending. See Appendix 3.

4. The Antibiotic Uses Covered by this Petition Are Not Consistent with the Criteria in Guidance #152

Format Note: The following discussion includes several excerpts of tables that are taken verbatim from Guidance #152. Those excerpts are shown in this typeface. The excerpts are identical to the Guidance except as noted by use of brackets; in addition, some footnotes have been omitted.

a. Overview

Guidance #152 lays out FDA's recommended approach to evaluating the safety of agricultural antibiotics with regard to creation of antibiotic-resistant bacteria of human health concern. Although the Guidance in several places uses terms such as “suggested” or “examples” of approaches, this Petition focuses on the substantive content of the Guidance, as indicating FDA’s best thinking on how these analyses should be performed, and on how identified risks should be managed to avoid unsafe outcomes.

Under the Guidance, use of a particular drug is assigned an overall “risk estimate” of High, Medium, or Low based on a qualitative risk assessment that has three components: release, exposure, and consequence.

- Release. How likely is the drug to be used in food animals in a way that engenders resistance?
- Exposure. How likely are the resistant organisms to make their way to humans?
- Consequence. How important are the drugs for human medicine?

In addition, the Guidance lays out a mechanism for integrating the results of these three assessments into an overall qualitative risk estimate of High, Medium, or Low.

The Guidance also describes risk management steps associated with high, medium, and low risks findings. Among others, these risk management steps include limitations on the extent of use (e.g., individual animal vs. herdwide/flockwide use).

Because this Petition addresses certain already-approved uses, it is convenient to start by considering the Guidance’s risk management strategies, before examining the components of the qualitative risk analysis. The following section presents an analysis of these provisions for the uses covered by this Petition.

b. Guidance #152 Allows Herdwide/Flockwide Use Only for “Low Risk” Antibiotics

Table 7 (p. 23) describes high “extent of use” as all flock-wide and herd-wide use, regardless of duration:

Table 7 (excerpt)

Duration of use	Intended administration to:		
	individual animals	select groups or pens of animals	flocks or herds of animals
Short (<6 days)	L ¹	M ²	H ³
Medium (6-21 days)	L	M	H
Long (>21 days)	M	H	H

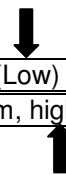
¹Low, ²Medium, and ³High extent of use

Next, Table 8 (p. 25) indicates that a “high” extent of use is *only* allowable for drugs that fall in Category 3 because they have a Low risk ranking; by contrast, “high” extent of use is *not* allowable for drugs in either Category 1 (High risk) or Category 2 (Medium risk):

Table 8 (excerpt)

Approval conditions	Category 1 (High)	Category 2 (Medium)	Category 3 (Low)
Extent of use ²	Low	Low, medium	Low, medium, high

²See Table 7 for characterization of extent of use



In summary, herdwide/flockwide use is allowable *only* for drugs with a Low risk ranking. As shown in the following section, the drugs covered by this Petition are not Low risk. Accordingly, their flock- or herd-wide use is inconsistent with the Guidance’s safety criteria.

c. The Antibiotics Covered by the Petition are Not “Low Risk”

Under the Guidance, a Low risk ranking occurs *only* under certain circumstances. As noted above, risk rankings are produced by integrating three separate qualitative assessments – “Release,” “Exposure,” and “Consequence.” “Consequence” means the importance of the drug in human medicine, and may be rated as Important, Highly Important, or Critically Important. As further discussed below, “Exposure” describes the likelihood of people to be exposed to antibiotic-resistant bacteria from food, and is rated

as High, Medium, or Low; “Release” involves whether agricultural use of the drug selects for resistant bacteria in the animal, and is also rated as High, Medium, or Low.

As shown below, the Release evaluation does not affect the overall Risk ranking for the drugs and uses covered by this Petition; in other words, the Consequence and Exposure evaluations alone will determine the outcome. To demonstrate this, it is useful to look first at the Consequence evaluation, then the Exposure evaluation, and then to consider how the two combine for the final Risk rating.

The Guidance defines drugs’ importance in human medicine as “critically” or “highly” important as follows (Table A1, pp. 30-33):

<p>Critically Important: Antimicrobial drugs which meet BOTH criteria 1 and 2 below.</p> <p>Highly Important: Antimicrobial drugs which meet EITHER criteria 1 or 2 below.</p> <ol style="list-style-type: none"><i>1. Antimicrobial drugs used to treat enteric [gut] pathogens that cause food-borne disease.</i><i>2. Sole therapy or one of few alternatives to treat serious human disease or drug is essential component among many antimicrobials in treatment of human disease.</i>⁴⁵

As shown in the following excerpt from the Guidance, the drugs covered by this petition all are ranked as “critically important” or “highly important.” Specifically, macrolides are “critically important,” while penicillins, aminoglycosides, clindamycin/lincomycin,⁴⁶ tetracyclines, glycopeptides, and streptogramins are “highly important.” One sulfonamide combination drug – namely trimethoprin/sulfamethoxazole⁴⁷ – is also designated as critically important (see discussion in section IV.C. below).

Table A1 (excerpt)

⁴⁵ In Petitioners’ view, this criterion is insufficiently protective of the public health, inasmuch as it fails to protect valuable drugs simply because there are more than a “few” alternative drugs at present. Given that resistance to existing antibiotics is spreading far more rapidly than new drugs are being developed, this approach is unwise. For purposes of this Petition, however, we employ the Guidance’s categorization of drugs.

⁴⁶ Table A1 lists clindamycin, which is essentially identical to lincomycin. Clindamycin is the primary form of the drug used in humans, while lincomycin is primarily used in animals. The two drugs differ by a single group: a hydroxyl group (OH) in lincomycin is substituted by a chlorine (Cl) in clindamycin. See “Antimicrobial Chemotherapy,” www.bmb.leeds.ac.uk/mbiology/ug/ugteach/icu8/antibiotics/protein.html (accessed Apr. 5, 2005).

⁴⁷ Guidance #152 uses the abbreviation “trimeth/sulfameth.” See Table A1.

	Classification	1) Enteric pathogen responsible for food-borne disease	2) Sole/limited therapy or essential therapy for serious disease (See "Comments" for examples)	3) Used to treat enteric pathogens in non-food-borne disease	4) No cross-resistance within class/no linked cross-resistance with other classes	5) Limited risk of transmission of resistance elements within/across species of organisms	Comments
Natural penicillins	H		X				Neurosyphilis: Serious infection due to Group A streptococci
Benzathine pen G							
Penicillin G							
Penicillin V							
Penase Resistant Pens	H		X				Serious infections due to <i>Staphylococcus aureus</i>
Cloxacillin							
Dicloxacillin							
Nafcillin							
Oxacillin							
Antipseudomonal Pens	H		X	X			Serious infections due to <i>Pseudomonas aeruginosa</i>
Mezlocillin							
Pipercillin							
Pipercillin/tazo							
Ticarcillin							
Ticarcillin/Clav							
Carbenicillin							
Aminopenicillins	H		X	X			Infections due to <i>Listeria monocytogenes</i>
Amoxicillin							
Ampicillin							
Ampicillin/Sulbacta							
Aminoglycosides	H		X	X			
Amikacin							
Gentamicin							Enterococcal endocarditis Sole antimicrobial approved for aerosolized therapy in cystic fibrosis
Tobramycin							
Kanamycin							
Streptomycin							Infections due to <i>Mycobacterium tuberculosis</i>
Neomycin							
Netilmicin							
Spectinomycin							Infections due to <i>Neisseria gonorrhoeae</i> in pregnancy
Macrolides	C	X	X				Legionnaire's disease: MAC/MAI prophylaxis and therapy
Erythromycin							
Azithromycin							
Clarithromycin							

							Serious infections due to Group A streptococci: Alternative therapy of infections due to <i>Staphylococcus aureus</i> in patients with serious beta lactam allergy
Clindamycin [Lincomycin]	H		X				
Tetracyclines	H		X				Rickettsial disease: Anthrax therapy/prophylaxis
Tetracycline							
Chlorteracycline							
Demeclocycline							
Doxycycline							
Minocycline							
Glycopeptides	H		X				Infections due to methicillin resistant <i>Staphylococcus aureus</i>
Vancomycin							
Streptogramins	H		X				Infections due to vancomycin resistant <i>Enterococcus faecium</i>
Dalfopristin/quinupristin							
Trimeth/Sulfameth	C	X	X	X			Infection due to <i>Pneumocystis carinii</i>

The next key factor is found in Table 6 of the Guidance (p. 21), which provides a grid of all possible combinations of the three assessments' ratings and the resulting risk ranking. Significantly, Table 6 indicates that Critically Important drugs *never* receive a Low risk ranking, while Highly Important drugs receive a Low risk ranking *if and only if* the Exposure and Release rankings are *both* Low.

Table 6 (excerpt)

Release	<u>Exposure</u>	<u>Consequence</u>	<u>Risk Estimation</u>
Low	Low	Highly important	Low
[Medium or High]	[Medium or High]	Highly important	[Medium or High]
[any]	[any]	Critically Important	[Medium or High]

The Exposure rating is a function of two factors: level-of-consumption and extent-of-contamination (p. 19).⁴⁸ Table 2 (p. 17) indicates that consumption of beef, chicken, and pork qualifies as a “High” consumption commodity:

⁴⁸ The Guidance’s exposure evaluation ignores all non-food pathways, though the Guidance notes in passing that “uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies” (p. 15). The Petitioners view the disregard of non-food pathways as another way in which the Guidance is less-than-protective of public health. For purposes of this Petition, however, we employ the Guidance’s exposure evaluation scheme, because the uses covered by this Petition are nonetheless inconsistent with even those less-than-protective criteria.

Table 2 (excerpt)

<u>Commodity</u>	<i>Per capita consumption</i> (pounds per capita per year)	Qualitative ranking
Beef	62.9	High
Chicken	53.9	High
Pork	46.7	High

The probability of exposure is then determined from Table 5. Under Table 5, if the amount of a food commodity consumed is High, the probability of exposure is always High or Medium (never Low), regardless of extent of contamination of the food commodity:

Table 5

	<u>Probability of human exposure to a given bacteria</u>		
	Amount of food commodity being consumed		
Amount of food commodity contamination	High	Medium	Low
High	H	H	M
Medium	H	M	L
Low	M	L	L

In other words, as a result of the “high” consumption rankings for beef, chicken and pork, the Exposure assessment from Table 5 *never* yields an Exposure ranking of Low. Accordingly, Table 6 shows that there is *no circumstance* that results in an overall Risk estimate of Low for any Highly Important drug.

Critically, because use of the drugs covered by this Petition in chicken, swine, or beef cattle *always* results in a High (Category 1) or Medium (Category 2) risk ranking, "high extent" uses of those drugs – which includes the herdwide/flockwide uses covered by this Petition – are not consistent with the risk management criteria set forth in the Guidance. As noted above and reiterated below, Table 8 (p. 25) indicates that a “high” extent of use is *only* allowable for drugs that fall in Category 3 because of having a Low risk ranking; by contrast, “high” extent of use is *not* allowable for drugs in either Category 1 (High risk) or Category 2 (Medium risk):

Table 8 (excerpt)

Approval conditions	Category 1 (High)	Category 2 (Medium)	Category 3 (Low)
Extent of use ²	Low	Low, medium	Low, medium, high

²See Table 7 for characterization of extent of use

d. The Status of Sulfonamides Under Guidance #152

Table A1 does not expressly list sulfonamides, but lists one specific member of the sulfonamides class – trimeth/sulfameth, which is ranked as “critically important.” Because other members of the sulfonamides class may cause cross-resistance to trimeth/sulfameth (a combination drug that works synergistically), FDA should also initiate and conclude proceedings to withdraw herdwide/flockwide uses of sulfonamides for 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) in chicken, swine, and beef cattle. FDA should evaluate all sulfonamides as “critically important” drugs for purposes of the Consequence assessment, and proceed to withdraw approvals for their use as described above absent persuasive evidence showing a lack of cross-resistance to trimeth/sulfameth.

e. Conclusion

In sum, the Petition is entirely consistent with the criteria in Guidance #152 in seeking the withdrawal of approvals for herdwide/flockwide uses of Critically Important and Highly Important antibiotics in chicken, swine, and beef cattle. Because herdwide/flockwide uses for growth promotion and routine disease prevention account for the preponderance of antibiotic use,⁴⁹ and because development of resistance is, in part, a function of the quantity of antibiotics used, FDA should promptly initiate and conclude withdrawals for herdwide/flockwide uses of critically and highly important antibiotics for 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).

C. Environmental Impact

FDA’s regulations indicate that withdrawals of drug approvals are among the class of actions that are “categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS.” 21 C.F.R. 25.33 & subsection (g).

⁴⁹ Mellon M, Benbrook C, Benbrook K. 2000. Hogging It!: Estimates of Antimicrobial Abuse in Livestock. Cambridge, MA: Union of Concerned Scientists. Available at www.ucsusa.org/food_and_environment/antibiotic_resistance/page.cfm?pageID=264 (accessed Apr. 5, 2005).

D. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

[original document signed]

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On behalf of petitioners Environmental Defense, American Academy of Pediatrics, American Public Health Association, Food Animal Concerns Trust, and Union of Concerned Scientists.

Appendix 1: Description of the Petitioners

Environmental Defense is dedicated to protecting the environmental rights of all people, including the right to clean air, clean water, healthy food, and flourishing ecosystems. From its founding in 1967, Environmental Defense has used an innovative mix of scientists, economists, and attorneys to devise practical solutions to environmental problems.

Founded in 1930, the **American Academy of Pediatrics** is an organization of 60,000 pediatricians committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents and young adults.

The **American Public Health Association** (APHA) is the oldest organization of public health professionals in the world, representing members from over 50 occupations of public health. APHA has been influencing policies and setting priorities in public health for over 125 years.

Founded in 1982, **Food Animal Concerns Trust** (FACT) advocates for farming practices that improve the safety of meat, milk, and eggs. FACT works to accomplish its goals through on-farm research projects, work with the federal regulatory agencies and Congress, and an ongoing review of the scientific literature.

Founded in 1969, **Union of Concerned Scientists** (UCS) is a non-profit partnership of scientists and citizens combining rigorous scientific analysis, innovative policy development, and effective citizen advocacy to achieve practical environmental solutions.

Appendix 2: FDA Has Not Previously Determined that the Antibiotics Covered By this Petition Meet Modern Scientific Standards for Safety with regard to Antibiotic Resistance.

When approvals for the antibiotic uses covered by this Petition were initially approved decades ago, FDA gave little consideration to safety issues involving antibiotic resistance.⁵⁰ In 1973, FDA issued regulations requiring antibiotics already on the market to undergo certain studies.⁵¹ These became known as the 558 studies, because the requirements were codified in section 558 of Part 21 of the Code of Federal Regulations.⁵²

However, there were major scientific flaws in the basic protocols for the required studies.⁵³ The Animal Health Institute (AHI), the trade association for animal-drug

⁵⁰ Indeed, it is not entirely clear exactly how those approvals were issued. As FDA has noted, “Under Section 108 of [the Animal Drug Amendments of 1968], any product that had been approved before 1968 ... would be considered to be the subject of an approved new animal drug application under the new section 512. ... The approval processes for these products before the 1968 amendments were complex, redundant, and involved the acceptance of secondary manufacturers/distributors, sometimes based on a demonstration of equivalence of their products to primary sponsor products and sometimes not. Unlike the current new animal drug application process under section 512 of the act, this was generally not an orderly process. As a result, the agency’s and sponsors’ ability to document the pre-1968 approvals has been hampered.” FDA, Proposed Regulation: New Animal Drugs; Removal of Obsolete and Redundant Regulations [21 CFR 510 and 558]. 68 Fed. Reg. 47272-47277 (Aug. 8, 2003). Available at <http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2003/03-20244.htm> (accessed Apr. 5, 2005).

⁵¹ 38 Fed. Reg. 9811 (April 20, 1973) (final rule). The proposed rule had been proposed a year earlier (37 Fed. Reg. 2444) (Feb. 1, 1972). FDA subsequently withdrew approvals for some drugs determined not to be in compliance with the data submission requirements of Sec. 558.15, at 41 Fed. Reg. 8282 (Feb. 25, 1976)). See 68 Fed. Reg. 47273 for a description of the history of Section 558.15.

⁵² The regulations were initially codified at 21 CFR 135.109, but were recodified at 21 CFR 558.15 in 1974.

⁵³ Bacteria are classified as either gram-positive or gram-negative, based on their appearance under the microscope after a certain stain is applied. Gram-positive bacteria are generally killed by a different set of antibiotics than are gram-negative bacteria. Donna U. Vogt and Brian A. Jacson, Congressional Research Service. “Antimicrobial Resistance: An Emerging Public Health Issue.” (Jan. 24, 2001) (pp. 3-4, note 9). The 558 studies tested whether certain antibiotics increased the resistance of the gram-negative bacteria *salmonella* and *E. coli* to a range of human-use antibiotics. However, 42 of the 44 drugs tested under this regime were drugs intended to treat gram-positive bacteria, resulting in “a mismatch between the drugs and the bugs.” Remarks of Jean Cooper, “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). As noted in the meeting transcript (p. 104), Dr. Cooper had previously been with the Center for Veterinary Medicine, but at the time of the meeting was Chief, Clinical Chemistry and Toxicology Branch, Centers for Devices in Radiological Health, FDA.

manufacturers, noted as much in summarizing the views of a public meeting on the 558 protocols:

“There was consensus that *in vivo* models, at least by current scientific knowledge, were **not considered of value** in predicting the rate and extent of resistance development and the impact this might have on public health....

“It was clearly concluded from the discussions at the workshop that **such studies are not predictive** ... AHI agrees with the conclusions of the workshop.”⁵⁴

As an FDA senior staffer put it, “These studies, as designed, are 30 years old. Science has moved on.”⁵⁵

In 2003, FDA proposed to repeal the portions of the section 558 regulations relating to these studies on the ground that they were “obsolete” and that “FDA has a new strategy and concept for assessing the safety of antimicrobial new animal drugs, including subtherapeutic use of antimicrobials in animal feed, with regard to their microbiological effects on bacteria of human health concern.”⁵⁶

⁵⁴ 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).

⁵⁵ J. Cooper, “558.15’ studies: A historical perspective,” p. 119. Available at www.fda.gov/cvm/Documents/CVM-PSES222.doc (accessed Apr. 5, 2005).

⁵⁶ FDA, Proposed Regulation: New Animal Drugs; Removal of Obsolete and Redundant Regulations [21 CFR 510 and 558]. 68 Fed. Reg. 47272-47277, 47276 (Aug. 8, 2003). Available at <http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2003/03-20244.htm> (accessed Apr. 5, 2005).

Additional attachments

[This page was not included with the hard-copy Petition as filed with FDA, but is included in the electronic version because Appendix 3 and the Addendum are contained in separate electronic files.]

Appendix 3. Letters from FDA to Manufacturers of Certain Antibiotic Feed Additives. [see separate PDF file]

Addendum. List of Covered Drugs. [see separate Excel file]