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

[2]See 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

[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).

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).

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]

Karen Florini, Senior Attorney
Environmental Defense
1875 Connecticut Ave., NW, Suite 600
Washington, DC 20009
phone: 202/387-3500 x3318
fax: 202/234-6049
kflorini@environmentaldefense.org

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

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[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]

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[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]

Appendix 3.
Letters from FDA to Manufacturers of Certain Antibiotic Feed Additives.