KEEP ANTIBIOTICS WORKING
The Campaign to End Antibiotic Overuse
www.KeepAntibioticsWorking.com

May 27, 2010

The Honorable Joshua M. Sharfstein, M.D.
Principal Deputy Commissioner
Food and Drug Administration
Bldg. 1, Rm. 2217
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Deputy Commissioner Sharfstein:

At our March 19 meeting you raised the issue of whether the Food and Drug Administration ("FDA") has the legal authority to revoke its approvals of the nontherapeutic use in food animals of medically important antibiotics. As discussed below, we believe that it clearly does.

I. In 2005 the FDA established a two-step legal standard for revoking antibiotic approvals.

In July 2005 FDA Commissioner Lester M. Crawford affirmed the 2004 decision of an Administrative Law Judge to revoke the FDA's approval of the use in poultry of Bayer's fluoroquinolone antibiotic enrofloxacin (the other manufacturer of enrofloxacin, Abbott Laboratories, voluntarily agreed in 2000 to stop selling it). Relying on the legal standards articulated in two federal court of appeals decisions, *Hess & Clark, Inc. v. FDA*, 495 F.2d 975, 992 (D.C. Cir. 1974), and *Rhone-Poulence, Inc. v. FDA*, 636 F.2d 750, 752 (D.C. Cir.)(1980)(*per curiam*), the Commissioner established a two-step legal standard on the burden of proof in such cases:

"In sum, with respect to the various issues raised by the participants on the burden of proof and standard of proof, I conclude that:

> [1] CVM bears an initial burden to produce evidence. CVM must show that there is a reasonable basis from which serious questions may be inferred about the ultimate safety of enrofloxacin use in poultry and any substance that may be formed in or on food as a result of such use.
>
> [2] If CVM carries its burden of production, Bayer, as the drug's sponsor, has the burden of persuasion on the ultimate question of whether enrofloxacin is shown to be safe. Bayer must do so, as set out in 512(d)(1)(A) with 'adequate tests by all methods reasonably applicable...' 21 U.S.C. § 360b(d)(1)(A).

PO Box 14590 • Chicago, IL 60614-0590
PHONE: 773-525-4952 • FAX: 773-525-5226 • E-MAIL: information@KeepAntibioticsWorking.com

As the fact finder, I must weigh the record evidence and make my factual findings based on the weight of the evidence. In other words, my findings must be supported by a preponderance of the evidence."[1]

Bayer did not exercise its legal right to appeal the Commissioner's decision to a federal court of appeals.

II. Applying the FDA's legal standard to the facts about the nontherapeutic use of penicillin in animal feed shows that such use is not safe.

A. FDA has shown "that there is a reasonable basis from which serious questions may be inferred about the ultimate safety" of giving penicillin to food animals.

In 1977 the FDA proposed to withdraw its approval for all uses of penicillin in animal feeds because new evidence showed that nontherapeutic use was not safe for people and that therapeutic use is not effective in food animals. 42 Fed. Reg. 43770 (August 30, 1977).

In 2004 the FDA sent letters to the three companies making penicillin for use in food animals (Alpharma Inc., Pennfield Oil Company, and Phibro Animal Health) asking them to present evidence that such use is safe for people.[2]

In September 2008 the FDA told the Senate Committee on Health, Education, Labor, and Pensions that it had completed its review of both its administrative files and the "scientific literature for microbial food safety information for penicillin-containing products" and that it "continues to have safety concerns regarding the non-therapeutic use of antimicrobial drugs in food-producing animals."[3] The FDA said that in its review it had applied the risk assessment principles set forth in its 2003 Guidance #152 ("Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern"), which the FDA adopted after extensive public comments.

In sum, the evidence on the safety of penicillin that the FDA has collected over three decades meets the first prong of the FDA's legal test – that is, CVM has "carried its burden of production" of evidence for a reasonable basis for safety concerns.

---

[1] http://www.regulations.gov/search/Regs/home.html#documentDetail?R=09000064804cddd9. at 8-9 (visited April 10, 2010).
[2] http://www.keepantibioticsworking.com/new/resources_library.cfm?RefID=107514 (visited May 26, 2010)
[3] http://www.keepantibioticsworking.com/new/resources_library.cfm?refID=104260. at 8 (visited April 12, 2010).

B. The sponsors of penicillin have not met "the burden of persuasion on the ultimate question of whether penicillin is shown to be safe."

It is our understanding that the three manufacturers of penicillin for use in food animals did not supply any information to the FDA in response to its 2004 letters. Nor are we aware of any published scientific studies showing that it is safe for humans to give penicillin to food animals[4].

In sum, the sponsors of penicillin have not met – and could not meet – their burden of showing by the preponderance of the evidence that the nontherapeutic use of penicillin in food animals is safe.

III. Conclusion

The time is ripe for the FDA to demonstrate through actions that it is serious about protecting the public health by accomplishing what it began more than thirty years ago: ordering the producers of penicillin to stop selling it for nontherapeutic use in food animals.

Sincerely,

Richard Wood
Steering Committee Chair
Keep Antibiotics Working

cc: Commissioner Margaret A. Hamburg, M.D.
Deputy Commissioner of Foods, Michael R. Taylor. J.D.
C.V.M. Director Bernadette M. Dunham, D.V.M., Ph.D.
Chief Counsel Ralph S. Taylor, J.D.

[4] The drug sponsor Alpharma funded a risk assessment that looked at a single outcome (death) from a small fraction (31,500) of the over 400,000 annual enterococcal infections in the U.S. and still found deaths associated with livestock use. The assessment did not include other potential pathogens and did not consider cross resistance with other beta-lactam drugs. Cox LA Jr, Popken DA, Mathers JJ. 2009. Human health risk assessment of penicillin/aminopenicillin resistance in enterococci due to penicillin use in food animals. Risk Anal. 2009 Jun;29(6):796-805.

PO Box 14590 • Chicago, IL 60614-0590
PHONE: 773-525-4952 • FAX: 773-525-5226 • E-MAIL: information@KeepAntibioticsWorking.com