

# SUPERBUG ME: THE FDA'S ROLE IN THE FIGHT AGAINST ANTIBIOTIC RESISTANCE

*Vanessa K.S. Briceño\**

## I.

### INTRODUCTION

For the first time, the United States Food and Drug Administration (FDA) has withdrawn approval for a livestock antibiotic based on concerns about the development of antibiotic-resistant illnesses in humans. This decision has serious implications not only for human health, but also for the growing domestic awareness of the effects of indiscriminate commercial use of antibiotics. Anti-microbial resistance can cause significant problems for human health: “ordinary” infections that have become resistant to a routine course of antibiotics can result in hospitalization and severe side-effects.<sup>1</sup> While organizations such as the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), and the European Union (EU) treat antibiotic resistance as an issue of major concern,<sup>2</sup> the FDA’s July 28, 2005 decision to withdraw approval for Baytril® marks the

---

\* Candidate for J.D., 2007, New York University School of Law; B.A. University of Texas at Austin, 2001. The author was a summer intern at Environmental Defense in 2005. The author wishes to thank Dr. Becky Goldberg and Karen Florini, Esq. at Environmental Defense for their invaluable guidance and support and Emily Blum-sack for her ever-patient editing.

1. See Centers for Disease Control and Prevention, *Get Smart Campaign: Antibiotic Resistance*, August 4, 2005, <http://www.cdc.gov/drugresistance/community/default.htm>; see also Karen Florini & Rebecca J. Goldberg, *Playing Chicken with Antibiotics*, 22 ENV’T’L FORUM 22, 22 (May/June 2005) (describing recent case in which thirteen-year-old boy underwent three operations and lost all hearing in one ear due to resistant bacterial infection).

2. See Centers for Disease Control and Prevention, *Get Smart Campaign: Background on Antibiotic Resistance*, August 4, 2005, <http://www.cdc.gov/drugresistance/community/>; World Health Organization, *Antimicrobial Resistance* (January 2002), <http://www.who.int/mediacentre/factsheets/fs194/en/>; Commission Regulation 1831/2003, art. 3, 2003 O.J. (L 268) 29 (EC) (legislation banning all use of non-therapeutic antibiotics and placing livestock antibiotics under control of veterinary medicine legislation which requires veterinarian’s prescription). The European Union has already banned use of all non-therapeutic antibiotics used in livestock. *Id.*

first U.S. government response to the issue.<sup>3</sup> The FDA primarily based its decision on concerns about antibiotic-resistant illnesses in humans,<sup>4</sup> and Bayer, the drug's sponsor and manufacturer, surrendered quickly to the decision, reinforcing the FDA's authority and legitimate grounds for the decision as well as the message that similar decisions will be difficult to contest in the future. There is also evidence that Congress has begun to involve itself in the move to ban certain livestock antibiotics.<sup>5</sup> This Recent Development will explain the basic difficulties presented by antibiotic resistance and how the international community and U.S. organizations have attempted to combat the problem. Most significantly, this piece will show that the recent FDA decision, combined with market pressures and congressional action, indicate that the United States has finally begun to seriously address an issue that has been recognized internationally as a major threat to human health.

## II.

### ANTIBIOTIC RESISTANCE

Antibiotics were revolutionary in the 1940s when they came into widespread use, and their development led to a marked increase in our ability to fight illness caused by bacterial infections.<sup>6</sup> Although there are numerous ways in which bacteria can become resistant to available antibiotics, one basic explanation is selection pressure. Mutations in DNA give some bacteria more resistance to available antibiotics.<sup>7</sup> These bacteria will survive a course of antibiotic treatment and subsequently reproduce, creating entire strains that will not respond to antibiotic treatment. One of the numerous places that bacteria can thrive

---

3. Keep Antibiotics Working, *Keep Antibiotics Working Praises FDA's First Ever Ban of Agricultural Drug Due to Antibiotic-Resistance Effects in Humans*, July 28, 2005, available at [http://www.keepantibioticsworking.org/new/resources\\_library.cfm?refID=73539](http://www.keepantibioticsworking.org/new/resources_library.cfm?refID=73539).

4. Withdrawal of Approval of New Animal Drug Application Enrofloxacin in Poultry, Docket No. 2000N-1571 (Dep't of Health & Human Servs. July 28, 2005) [*hereinafter* Final Decision].

5. Florini & Goldberg, *supra* note 1, at 29 (citing slowness of FDA withdrawal process as motivating Congress to introduce bipartisan legislation withdrawing approval for all medically-important antibiotic growth promoters).

6. CENTERS FOR DISEASE CONTROL AND PREVENTION, PREVENTING EMERGING INFECTIOUS DISEASES: ADDRESSING THE PROBLEM OF ANTIMICROBIAL RESISTANCE, A STRATEGY FOR THE 21ST CENTURY 2 (1998), available at <http://www.cdc.gov/ncidod/emergplan/antiresist/antimicrobial.pdf>. By the mid-1940s, antibiotics were also used for livestock. Human-Use Antibiotics in Livestock Production, [http://www.fda.gov/cvm/HRESP106\\_157.htm#background](http://www.fda.gov/cvm/HRESP106_157.htm#background) (last visited Jan. 14, 2006).

7. Center for Veterinary Med., Food & Drug Admin., *Animation Narration: Antimicrobial Resistance*, Aug. 2004, [http://www.fda.gov/cvm/cvm\\_scriptanimation.htm](http://www.fda.gov/cvm/cvm_scriptanimation.htm).

is within livestock and animal tissue. Not all bacteria are killed during meat processing, however, and resistant bacteria in livestock can be passed to humans when the meat is consumed. Human infection with these strains can result in hospitalization, severe and possibly permanent illnesses, and even death.<sup>8</sup>

A. *Agricultural Antimicrobial Use Contributes Significantly to Antibiotic Resistance*

Antibiotic resistance is “among CDC’s top concerns” and “has been called one of the world’s most pressing health problems.”<sup>9</sup> According to the WHO, a main source of resistant bacteria is the overuse of antibiotics in animals,<sup>10</sup> and the WHO has issued global guidelines on how to contain antimicrobial resistance developing in animals raised for food.<sup>11</sup> The vast majority of livestock antibiotics “are administered . . . for ‘non-therapeutic’ purposes; i.e., to promote slightly faster growth and to prevent disease . . . .”<sup>12</sup> The WHO strongly advocates eliminating the use of these antibiotic growth promoters (AGPs), which are primarily used to “control[ ] excess bacteria in the digestive tract of an animal, which is a normal response to a grain-based diet. Animals grow more quickly and efficiently and have better overall well-being because health maintenance antibiotics also suppress disease.”<sup>13</sup> Unlike therapeutic uses, which treat an animal for a particular illness, AGPs are administered to the entire group to reduce other maintenance and production costs.

Any kind of antibiotic usage can lead to resistant bacterial strains,<sup>14</sup> and one possible solution is to lessen overall usage. Not all antibiotic usage results in resistant strains at equal rates, however. Inadequate dosage or a dosage which does not kill all of the bacteria is

---

8. See Final Decision, *supra* note 4, at 19–20 (listing effects from lasting *Campylobacter* infections, including meningitis, peritonitis, blood poisoning, reactive arthritis, and Guillian-Barré Syndrome, which is “characterized by a sudden onset of paralysis that in 20–30% of cases leaves patients unable to breathe without a respirator.”)

9. Centers for Disease Control and Prevention, *supra* note 2.

10. World Health Organization, *supra* note 2.

11. WORLD HEALTH ORGANIZATION, GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE, EXECUTIVE SUMMARY, 9–10 (2001), available at <http://www.who.int/drugresistance/guidance/en/index.html>. A few facets of the strategy relating to agricultural use include mandatory prescriptions for antimicrobial use in animals, the creation of national monitoring systems, and monitoring the development of resistant strains for swift corrective actions. *Id.*

12. Florini & Goldberg, *supra* note 1, at 23.

13. Animal Health Institute, *Keep Animals Healthy: Protecting a Healthy Food Supply*, <http://www.ahi.org/protecting/index.asp> (last visited Nov. 3, 2005).

14. World Health Organization, *supra* note 2.

as problematic as overuse.<sup>15</sup> Long-term, low doses of antibiotics expose huge numbers of animals, and therefore bacteria, to sub-therapeutic levels of antibiotics.<sup>16</sup> The benefit to livestock and the livestock industry from AGPs is marginal at best—a study of Denmark after the livestock industries voluntarily stopped using AGPs in 1998 showed that the production costs rose by just over one percent for pig livestock and resulted in no net cost increase for poultry.<sup>17</sup> While there was an increase in the number of infections requiring antimicrobial treatment in some animals,<sup>18</sup> some scientists believe that the loss of AGPs as a cheap fix for the industry will force them to maintain more sanitary facilities, leading to an overall increase in efficiency and animal health.<sup>19</sup> Therapeutic and non-therapeutic antibiotics for livestock account for roughly thirty-five to eighty-five percent of all antimicrobials used in the United States.<sup>20</sup>

Some antibiotics given to livestock are significant in human medicine,<sup>21</sup> which means that some food-borne bacterial infections will be specifically resistant to antibiotics administered to human patients. While any antibiotic resistance is cause for concern, scientists and lobbyists have become increasingly alarmed at resistance to antibiotics which are significantly used in human medicine.<sup>22</sup> One such

15. *Id.*

16. *Id.*; see also World Health Organization, *Use of Antimicrobials Outside Human Medicine and Resultant Antimicrobial Resistance in Humans*, <http://www.who.int/mediacentre/factsheets/fs268/en/> (Jan. 2002) [*hereinafter Use of Antimicrobials*] (explaining widespread overuse of antibiotics in livestock and how it contributes to resistance).

17. World Health Organization, *Impacts of Antimicrobial Growth Promoter Termination in Denmark 7* (2002), available at <http://www.who.int/salmsurv/en/Expertsreportgrowthpromoterdenmark.pdf>.

18. *Id.*

19. COMMITTEE ON DRUG USE IN FOOD ANIMALS, NAT'L ACADEMY OF SCIENCES, *THE USE OF DRUGS IN FOOD ANIMALS: BENEFITS AND RISKS* 181 (1999), available at <http://books.nap.edu/books/0309054346/html/181.pdf>.

20. MARGARET MELLON ET AL., *HOGGING IT: ESTIMATES OF ANTIMICROBIAL USE IN LIVESTOCK* 60 (Union of Concerned Scientists) (2001). The huge disparity in numbers comes from the fact that two different groups are providing them. The Union of Concerned Scientists estimates livestock antimicrobial use to account for up to eighty-four percent of all antimicrobial use in the U.S. *Id.* The Animal Health Institute (AHI), made up primarily of pharmaceutical companies, cites numbers closer to thirty-five percent of total U.S. antimicrobial production. *Id.*

21. *Use of Antimicrobials*, *supra* note 16.

22. Citizen Petition to the FDA, *Citizen Petition Seeking Withdrawal of Approvals of Certain Herdwide/Flockwide Uses of Critically and Highly Important Antibiotics Pursuant to Guidance #152* (Apr. 7, 2005) (on file with *NYU Journal of Legislation and Public Policy*) (classifying all currently approved animal antibiotics by their "risk" based on importance to human medicine, antibiotic resistance from drug's agricultural use, and likelihood of resistant bacteria reaching humans). The Petition spe-

example is enrofloxacin, a fluoroquinolone which is the key ingredient in Baytril® and an antibiotic that combats the presence of *E. coli* and other bacteria found in poultry.<sup>23</sup> Although fluoroquinolones had been used to treat *Campylobacter* infections in humans since 1986, it was not until they were used in poultry that scientists began to notice an increase in the number of resistant *Campylobacter* infections in humans.<sup>24</sup> Enrofloxacin was approved for use in poultry in 1996.<sup>25</sup> By 1998, the number of resistant infections had reached 13.6% of the total number of *Campylobacter* infections, and the next year it had reached 17.6%.<sup>26</sup> This increase, based on the agricultural use, was enough to propel the Center for Veterinary Medicine (CVM)<sup>27</sup> to recommend withdrawal of the drug in poultry, even though it had only been in use for four years;<sup>28</sup> this is a fairly rapid turnaround for a generally slow-moving agency.

While the FDA Decision to withdraw approval for Baytril® use in poultry deals with an antibiotic used therapeutically, as opposed to use for growth promoting purposes, there are some significant aspects which make this decision key to both uses. First, Baytril® was the only antibiotic approved for use in poultry containing enrofloxacin.<sup>29</sup> Second, evidence of a single occurrence of *E. coli* or fowl cholera in any one member of a poultry population prompts the introduction of the drug into the house drinking supply, thereby administering it to the entire flock.<sup>30</sup> This means that many animals which may not have been infected with the disease will still get a course of antibiotics. Furthermore, because the dosage is not individually tailored to the sick

---

cifically requests only the withdrawal of antibiotics considered “critically” or “highly” important to human medicine. *Id.*

23. Final Decision, *supra* note 4, at 22.

24. Center for Veterinary Medicine, Food & Drug Admin., *CVM Update: FDA/CVM Proposes to Withdraw Poultry Fluoroquinolones Approval*, (Oct. 26, 2000), [http://www.fda.gov/cvm/CVM\\_Updates/nooh.htm](http://www.fda.gov/cvm/CVM_Updates/nooh.htm) [*hereinafter Proposal to Withdraw Fluoroquinolones Approval*].

25. *Id.*

26. *Proposal to Withdraw Fluoroquinolones Approval*, *supra* note 24. Unlike the 1998 figure, which reflects measurements for all *Campylobacter*, the 1999 figure of 17.6% reflects measurements for the *C. Jejuni* strain alone. *Id.*

27. The Center for Veterinary Medicine is a branch of the FDA that regulates and monitors feed additives and drugs administered to animals. U.S. Food and Drug Administration, *Information About Center for Veterinary Medicine*, <http://www.fda.gov/cvm/aboutcvm.html> (last visited Jan. 11, 2006).

28. *Proposal to Withdraw Fluoroquinolones Approval*, *supra* note 24.

29. See Final Decision, *supra* note 4, at 4 n.1 (three applications for fluoroquinolones to be used in poultry were approved in total, only one of which was for enrofloxacin).

30. *Id.* at 22. In the context of commercially grown poultry, “it is not feasible or practical to administer enrofloxacin to individual birds.” *Id.*

animal, it is possible that the infected birds will be under-dosed.<sup>31</sup> The bacteria which are able to hold out the longest against the drug—those which are more prone towards fluoroquinolone resistance—will therefore be able to survive and multiply.<sup>32</sup> This type of therapeutic practice is thereby comparable to many AGP usages, and is one of the more worrisome exploitations of antibiotics currently allowed.

*B. Reducing Non-vital Antibiotic Use Is the Only Viable Means of Reducing Antibiotic Resistance*

A mandatory reduction in AGP use may seem like a fairly dramatic recourse, especially given how pervasive the practice is, but currently this is the primary reliable method of addressing problems of antibiotic resistance. As the incidence of resistant infections increase, doctors will probably become less inclined to prescribe fluoroquinolones for any *Campylobacter* infection, even though no other treatments have proven effective.<sup>33</sup> Additionally, pharmaceutical companies are unlikely to pursue the development of new antibiotics designed to respond to these “superbugs” because economic factors, as well as scientific limitations, make their development of limited value. Entirely new strains of antibiotics are difficult to discover—only two have been created in the past thirty years.<sup>34</sup> The problem is compounded by the fact that specific antibiotics are not very profitable for pharmaceutical companies: a drug that must be administered for long-term treatment or maintenance, such as insulin or an anti-depressant, generates more reliable returns than antibiotics, which are dispensed for only a single course of therapy.<sup>35</sup> The possibility that bacteria will become resistant to new antibiotics, thus rendering them useless, also reduces the profitability of developing new antibiotics.<sup>36</sup> The most effective approach to combating the development of superbug strains is to reduce the use of antibiotics, especially in cases where they are unnecessary. Further justifying this course of action is the fact that, in practice, simply reducing the amount of antibiotic use has considerably decreased the incidence of resistant bacterial strains.<sup>37</sup>

---

31. *Id.* at 22–23.

32. *Id.* at 23.

33. *Id.* at 54.

34. Florini & Goldberg, *supra* note 1, at 26.

35. *Id.*

36. *Id.*

37. *Id.* at 29.

## III.

INDUSTRY AND INTERNATIONAL RESPONSES TO  
ANTIMICROBIAL RESISTANCE

While the United States has only just begun to move against antibiotic resistance, various powerful entities have already put forth such efforts. The European Union has passed legislation banning all non-therapeutic antibiotics in livestock.<sup>38</sup> Perhaps even more surprisingly, a few large-scale meat purchasers discussed below have implemented purchasing policies that put both economic incentives and social pressure on livestock producers to stop use of medically significant antibiotics.

*A. Major Industry Pressure Will Motivate Livestock Producers to Decrease Their Use of AGPs*

Because the major proponents of AGPs favor them for largely economic reasons, it makes sense that economics should play a role in their demise. Producers hope to recoup their investment by sustaining production, and many livestock producers consider AGPs to be a cheaper alternative to overhauling their facilities to ensure healthier conditions. Some major meat purchasers, however, have implemented policies to favor or solely deal with livestock producers that limit the use of antibiotics.<sup>39</sup> McDonald's, one of the largest meat purchasers in the world,<sup>40</sup> has implemented a purchasing policy by which it will only accept chicken that is raised without any medically-important antibiotics used for non-therapeutic purposes.<sup>41</sup> McDonald's also will preference other meat suppliers who comply with these policies.<sup>42</sup> Another large catering company, Bon Appétit, has an even stronger restriction: they ban all use of non-therapeutic antibiotics in the poultry they purchase, not only medically important ones.<sup>43</sup> These economic pressures contribute to the U.S. movement towards awareness of agricultural antibiotic abuse—if the major meat purchasers refuse

---

38. *See supra* note 2.

39. *Id.* at 26–27.

40. *Id.*

41. Press Release, McDonald's Corp., McDonald's Global Policy on Antibiotic Use in Food Animals (June 2003), available at [http://www.mcdonalds.com/corp/values/socialrespons/market/antibiotics/global\\_policy.html](http://www.mcdonalds.com/corp/values/socialrespons/market/antibiotics/global_policy.html).

42. *Id.* McDonald's policy is mandatory for suppliers it has a "direct" relationship with (i.e., poultry suppliers), while the "indirect" relationship suppliers of beef and pork will receive preferential treatment for curbing antibiotic use. Part of the reason for this dual policy could be that there is a limited supply of antibiotic-free beef and pork. *See* Florini & Goldberg, *supra* note 1, at 27.

43. Florini & Goldberg, *supra* note 1, at 27.

to buy meat raised with non-therapeutic antibiotics, the livestock industry will certainly have to consider the cost in sales from their continued use.

*B. The European Union's Ban on AGPs Provides  
a Useful Model for the U.S.*

While corporations have begun to take action, so have other nations. In 2003, the European Union passed legislation banning all use of AGPs beginning in 2006,<sup>44</sup> although this is only the most recent legislative action in Europe. Sweden initiated this movement in 1986 by independently banning all use of AGPs, including those antibiotics not used in human medicine.<sup>45</sup> This was followed by similar all-encompassing bans in Denmark in 1999 and Switzerland in 2000,<sup>46</sup> although as members of the EU, both countries had been banning AGPs on a case-by-case basis before then.<sup>47</sup> The European Union started selectively banning individual antimicrobial products in 1997, and banned approximately eighteen before instituting a complete ban on all AGPs in 2003, regardless of whether or not they were significant for human medicine.<sup>48</sup> While two major pharmaceutical companies, Alpharma and Pfizer, tried to challenge the bans in EU courts, both claims were rejected.<sup>49</sup> No other company or group has tried to challenge the regulations since then.

---

44. Commission Regulation 1831/2003, art. 3, 2003 O.J. (L 268) 29 (EC).

45. *Use of Antimicrobials*, *supra* note 16.

46. *Id.*

47. Press Release, European Commission, Questions and Answers on Antibiotics in Feed (Mar. 25, 2002), <http://europa.eu.int/rapid/pressReleasesAction.do?reference=MEMO/02/66&format=PDF>.

48. *See* European Commission, Food and Feed Safety, Animal Nutrition, Feed Additives, Withdrawal of Authorisations, [http://europa.eu.int/comm/food/food/animal\\_nutrition/feedadditives/authorwithdrawal\\_en.htm](http://europa.eu.int/comm/food/food/animal_nutrition/feedadditives/authorwithdrawal_en.htm) (last visited Feb. 10, 2006); *see also supra* note 44 and accompanying text.

49. Case T-70/99, Alpharma, Inc. v. Council of the Eur. Union, 2002 E.C.R. II-3495; Case T-13/99, Pfizer Animal Health SA v. Council of the Eur. Union, 2002 E.C.R. II-3305. In both cases, the Court of First Instance held that preventative measures may be taken even when the "reality and seriousness" of the risks involved have not become fully apparent, such as with mad cow disease. In both cases, although the link between AGPs and antibiotic resistant illnesses in humans was not certain, there were sufficient concerns about human health that a ban on the products was not a "disproportionate measure." Press Release Number 71/02, The Court of First Instance Upholds The Council's Decision to Ban the Use of Certain Antibiotics as Additives in Animal Feed and Sets Out the Conditions on which the Precautionary Principle May Be Applied (Sept. 11, 2002), <http://www.curia.eu.int/en/actu/communiqués/cp02/aff/cp0271en.htm>.



IV.  
THE FDA DECISION

A. *The Process Leading to the Final Decision*

The domestic movement to ban enrofloxacin, the key component of Baytril®, began in 1999 when Center for Veterinary Medicine (CVM) issued their final advisory report on the possible antimicrobial resistance effects of using enrofloxacin in animals.<sup>50</sup> Ten months later, CVM issued an official proposal to withdraw approval for antimicrobials containing enrofloxacin used in poultry, thus initiating the withdrawal process.<sup>51</sup> The FDA granted Bayer's request for a formal evidentiary hearing, and the process took over two years from the time that the hearing was granted until the Administrative Law Judge finally issued his decision upholding the FDA's decision.<sup>52</sup> Bayer appealed to the FDA Commissioner, and another full year passed before a final decision was handed down.<sup>53</sup>

In the meantime, the FDA issued Guidance #152, a non-binding statement to the pharmaceutical industry on a possible method for evaluating the safety of new antimicrobial animal drugs.<sup>54</sup> The Guidance states the FDA's intention to evaluate the impact on human health for all uses of new agricultural antimicrobial drugs, specifically looking to food-borne pathogens and antimicrobial resistance.<sup>55</sup> Additionally, the Guidance contains the FDA's acknowledgement that agricultural antibiotic use is a point of concern in the overall issue of resistant illnesses in humans: "The FDA believes that human exposure through the ingestion of antimicrobial resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged . . . as a consequence of antimicrobial drug use in animals."<sup>56</sup> The FDA recommended that sponsors of new drugs evaluate their proposed animal drugs on the basis of three criteria—release, exposure, and consequence—and the drug

---

50. Center for Veterinary Medicine, Food & Drug Admin., *CVM Update: Antimicrobial Resistance Documents Available* (Dec. 8, 1999), [http://www.fda.gov/cvm/CVM\\_Updates/raupdate.html](http://www.fda.gov/cvm/CVM_Updates/raupdate.html).

51. *Proposal to Withdraw Fluoroquinolones Approval*, *supra* note 24.

52. Final Decision, *supra* note 4, at 5; *see also* Florini & Goldberg, *supra* note 1, at 28.

53. Final Decision, *supra* note 4; *see also* Florini & Goldberg, *supra* note 1, at 28.

54. Div. of Human Food Safety, Center for Veterinary Medicine, Food & Drug Admin., Guidance for Industry #152 (Oct. 23, 2003), *available at* <http://www.fda.gov/cvm/guidance/fguide152.pdf>.

55. *Id.* at 3.

56. *Id.*

would then be given a cumulative rating of high, medium, or low risk.<sup>57</sup>

*B. The FDA's Authority for the Decision and Burden Shifting*

The FDA's authority to approve the use of antibiotics is based upon the language of the Federal Food, Drug and Cosmetic Act (FFDCA).<sup>58</sup> Specifically, with regard to animal drugs, the FFDCA cites human health as one of the primary factors for FDA decision making, regardless of whether the drug is intended for humans or animals.<sup>59</sup> In animal drug withdrawal proceedings, the FDA, or one of its divisions, generally initiates the withdrawal and has the initial burden of production.<sup>60</sup> The burden is imposed by 21 U.S.C. § 360b(e)(1)(B), also called the "safety clause," which gives the FDA Commissioner the authority to withdraw approval for animal drugs whenever "new evidence . . . evaluated together with the evidence available . . . when the application was approved, shows that such drug is not shown to be safe for use . . . ."<sup>61</sup> Courts have interpreted this to mean that the FDA has the initial burden,<sup>62</sup> and must show that there are "serious questions" as to a drug's safety.<sup>63</sup> To raise "serious questions" regarding a drug's safety, the FDA must provide a "reasonable basis from which serious questions about the ultimate safety of [a drug] may be inferred."<sup>64</sup> The Commissioner adds that this standard

57. *Id.* at 6. The three criteria are: Release, or the probability that resistant bacteria will result from the drug's use; Exposure, the probability that humans will ingest the resistant bacteria from the source in question; and Consequence, the probability that human exposure to the resistant bacteria will result in adverse health conditions. *Id.*

58. Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301–399 (2000).

59. *See id.* § 360b(e)(1)(B) (giving Secretary of Health and Human Services authority to withdraw approval for animal drugs if new evidence shows them to be unsafe); *see also id.* § 321(u) (defining word "safe" as used in § 360b to include human and animal health).

60. Proposal to Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry, Docket No. 00N-1571, at 5 (Dept. of Health & Human Servs., Mar. 16, 2004) available at <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031604/00n-1571-idf0001-vol389.pdf> [*hereinafter* Initial Decision] (initial decision of Commissioner).

61. 21 U.S.C. § 360b(e)(1)(B).

62. *Hess & Clark, Inc. v. FDA*, 495 F.2d 975, 992 (D.C. Cir. 1974) ("The statute plainly places on the FDA an initial burden to adduce the 'new evidence' and what that new evidence 'shows.'").

63. *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752 (D.C. Cir. 1980) ("[The court must] determine whether the FDA has presented new evidence raising questions about the safety . . . that are sufficiently serious . . . .").

64. Initial Decision, *supra* note 60, at 5. This standard, which was proposed by CVM and accepted by the ALJ in the Initial Decision, was also officially adopted by the Commissioner in the Final Decision as the standard by which a withdrawal proceeding will be evaluated. Final Decision, *supra* note 4, at 7.

for the initial burden of production “has already been well established by Final Decisions concerning prior new animal drug approval withdrawals.”<sup>65</sup> Once the FDA has met the burden of production, the burden of persuasion shifts to the drug’s sponsor to show that the drug is safe.<sup>66</sup> The drug’s safety, both in human and animal health, must be evaluated by the initial approval standards set forth in the FFDCA: “adequate tests by all methods reasonably applicable.”<sup>67</sup>

The Final Decision of the Commissioner to withdraw approval for Baytril®, announced on July 28, 2005, explained that the available scientific studies on enrofloxacin and resistant *Campylobacter* infections support the decision.<sup>68</sup> Bayer argued that the CVM incorrectly developed its risk-assessment methods in 2000, and that it “‘assumes, but does not show, that poultry is a source of fluoroquinolone-resistant campylobacteriosis.’”<sup>69</sup> While no single study conclusively proves that resistant *Campylobacter* in poultry is causing infections in humans, the Commissioner considered the cumulative evidentiary implications of the scientific studies, which have linked enrofloxacin use to resistant *Campylobacter* in poultry and established poultry consumption as a risk factor for resistant campylobacteriosis infections in humans.<sup>70</sup> This, combined with the potential severity of treatment failure in humans, was enough to convince the FDA that the risks associated with continuing use of the drug were too great to justify its use in the market. In fact, the “FDA is not authorized . . . to weigh economic, health or other benefits that the drug provides against a health risk to the ultimate human consumers . . . .”<sup>71</sup> Unless the drug manufacturer can affirmatively show the drug safe for human health, no cost-benefit analysis will be considered.

---

65. Final Decision, *supra* note 4, at 8.

66. *Id.* at 8–9; *see also Hess & Clark, Inc.*, 495 F.2d at 992.

67. 21 U.S.C. § 360b(d)(1)(A) (2000) (stating grounds for approval or denial of animal drug application, including definition of “substantial evidence” standard by which applications must be evaluated); *see also Hess & Clark, Inc.*, 495 F.2d at 992.

68. Final Decision, *supra* note 4, at 23–24, 53–57. For example, some of the studies cited show that resistant bacteria appear in poultry populations that are treated with enrofloxacin, and others show a link between resistant illnesses in humans and poultry consumption. *Id.*

69. *Id.* at 65 n.92. CVM was required to submit a risk-assessment on the dangers of enrofloxacin for the initial withdrawal proposal. Bayer argued that CVM was required to demonstrate actual harm to human health, but the FDA Commissioner ultimately held that this formulation of the CVM’s burden was incorrect. *Id.* at 7.

70. *Id.* at 22–52.

71. *Id.* at 120.

### C. *The Significance of the Withdrawal*

In light of the effects on human health, the withdrawal of FDA approval for Baytril® may seem like an unsurprising result. However, this is the first time the FDA has issued such a decision based on concerns about antibiotic use in animals contributing to resistant illnesses in humans,<sup>72</sup> and sets a precedent by which future decisions on drugs used in livestock may be analyzed. The FDA does nothing especially new with the opinion—the well-defined burden shifting for animal drug withdrawal proceedings was followed, and their basis for jurisdiction is solidly founded in the language of the FFDCA. However, the FDA opened up the inquiry to include not only direct effects on human health but the indirect effects of antibiotic resistance. Because the decision recognizes the link between antibiotic resistance in animals produced for food and resistant illnesses in humans as a legitimate and serious concern, it sets a precedent for future withdrawals. Although Bayer petitioned the FDA for a stay on the order, its request was denied on the ground that the company had not shown they had sustained any irreparable harm under the criteria of 21 C.F.R. 10.35(e).<sup>73</sup> Two days later, Bayer indicated that they were not planning to pursue the fight in federal court, and would begin pulling Baytril® off of shelves and issuing refunds to purchasers.<sup>74</sup> Bayer had been fighting the proposed ban since 2000 when the CVM originally recommended it.<sup>75</sup> Their swift capitulation to the FDA's final decision, combined with the decisive ruling against Alpharma and Pfizer in the EU court system, suggests that pharmaceutical companies may be preparing to accept these new precedents as they develop further products.

The legislature has also gotten involved. Although the FDA ruling is certainly favorable, it took five years to come to fruition, and it is only the third contested withdrawal proceeding for agricultural

---

72. Press Release, Keep Antibiotics Working, Keep Antibiotics Working Praises FDA's First Ever Ban of Agricultural Drug Due to Antibiotic-Resistance Effects in Humans (July 28, 2005), [http://www.keepantibioticsworking.org/new/resources\\_library.cfm?refID=73539](http://www.keepantibioticsworking.org/new/resources_library.cfm?refID=73539).

73. *Washington in Brief: FDA Rejects Request on Animal Antibiotic*, WASH. POST, Sept. 7, 2005, at A8; Denial of Stay Petition, Letter from Lester M. Crawford, Comm'r of Food & Drugs, to Robert B. Nicholas, Counsel for Bayer (Sept. 2, 2005) (on file with author); see also 21 C.F.R. § 10.35(e) (2005) (requiring, among other factors, that petitioner "will otherwise suffer irreparable injury").

74. Press Release, Keep Antibiotics Working, Bayer Commended for Ending 5-Year Opposition to FDA Ban on Use of Cipro-like Antibiotics in Poultry (Sept. 7, 2005), [http://www.keepantibioticsworking.com/new/resources\\_library.cfm?refID=76541](http://www.keepantibioticsworking.com/new/resources_library.cfm?refID=76541).

75. See *Proposal to Withdraw Fluoroquinolones Approval*, *supra* note 24.

drugs that has been completed in FDA history.<sup>76</sup> Recognizing that a more efficient remedy is necessary to deal with the problem of antibiotic resistance, Congress has begun to consider legislation which would sidestep FDA-initiated withdrawal proceedings. Bills have been proposed in both houses of Congress which would require all medically-important AGPs to lose their approval two years after the bill is passed, unless the FDA makes a decision declaring a particular drug to be safe for continued use.<sup>77</sup> This interest from the legislature shows that the issue is finally receiving the attention it so urgently requires.

## V.

### CONCLUSION

The crisis of antibiotic resistance has already received international attention, but the United States has been lagging behind the global community. Now that the United States is acting on the issue, however, it seems like our comprehensive approach will result in a more effective policy on agricultural antibiotic use. The combination of the FDA ruling, the consideration by Congress, and the economic pressure from market forces like McDonald's, may indicate that the United States is finally beginning to take the problem of antibiotic resistance seriously.

---

76. See Florini & Goldberg, *supra* note 1, at 28. The other two successful withdrawals took, respectively, six years and two *decades* to complete. *Id.*

77. Preservation of Antibiotics for Medical Treatment Act of 2005, S.742, 109th Cong. (2005); Preservation of Antibiotics for Medical Treatment Act of 2005, H.R. 2562, 109th Cong. (2005).

