

August 26, 2005

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

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In the Matter of:

**Enrofloxacin for Poultry:
Withdrawal of Approval of
New Animal Drug Application
NADA 140-828**

FDA DOCKET: 00N-1571

PETITION FOR STAY OF ACTION

Pursuant to 21 CFR § 10.35, the undersigned entities submit this petition requesting that the Commissioner of Food and Drugs stay the effective date of the Final Decision and Order in the above-captioned matter.

The undersigned entities are as follows and are collectively referred to herein as "Petitioners":

The American College of Poultry Veterinarians is a specialty board of doctors of veterinary medicine that seeks to further educational and scientific progress in the field of poultry veterinary medicine; to promote the development of poultry veterinary medicine as a science; to improve and strengthen the instruction in poultry veterinary medicine; and to establish publication, testing, and continuing education requirements for the certification of poultry veterinarians.

The American Association of Avian Pathologists is a membership organization comprised of primarily graduate veterinarians specializing in private or commercial poultry practice, academic research, or allied industry employment providing technical services and/or

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research in avian medicine. AAAP provides externship experience in the field of avian medicine for new veterinary graduates and facilitates post-graduate advanced degree training through land grant universities for Masters or Ph.D. level training programs.

The Association of Veterinarians In Turkey Production is comprised of individuals who possess a degree in veterinary medicine and are full-time salaried employees of production companies raising market type turkeys and/or breeder type turkeys.

The Association of Veterinarians in Broiler Production is an organization whose members are licensed veterinarians employed by companies whose primary business function is the production and sale of chicken broilers.

The Association of Poultry Primary Breeder Veterinarians is comprised of veterinarians who work for poultry primary breeding companies that supply genetic breeding stock to integrated poultry companies in the egg and poultry meat industries. The association's mission is to have a forum for addressing and resolving the specialized needs of primary poultry breeding companies and the elite genetic lines owned by these companies.

A. Decision Involved

Petitioners seek a stay of the effective date of the Order published in the Federal Register effectuating the Commissioner's Final Decision in Docket No. 2000N-1571, *Withdrawal of Approval of the New Animal Drug Application for Enrofloxacin in Poultry*, signed on July 27, 2005. The Order in question is *Animal Drugs, Feeds, and Related Products; Enrofloxacin for Poultry; Withdrawal of Approval of New Animal Drug Application*, 70 FR 44048 (Aug. 1, 2005).

B. Action Requested

Petitioners request that the Commissioner stay the effective date of the above-referenced Final Decision and Order. A stay is needed because the poultry industry will soon enter the time

of year when poultry run the greatest risk of the type of respiratory illness for which enrofloxacin is approved.

A stay is also warranted pending the resolution of any petition for judicial review of this matter that the Animal Health Institute or Bayer Corporation (hereinafter referred to collectively as “Respondent-Participants”) may file and that the stay be effective until the completion of any action required as a result of that court’s review and decision. Under 21 U.S.C. § 355(h), the Respondent-Participants do not need to file a petition for judicial review until September 25, 2005, nearly two weeks after the effective date of the Order.

In the alternative, should the Commissioner believe that a stay pending judicial review is not warranted, Petitioners request that the Commissioner issue a temporary stay of the above-referenced Final Decision and Order to allow the Respondent-Participants to move the D.C. Circuit for a stay pending judicial review and that such temporary stay be effective until the court has ruled on said motion for a judicial stay. Such temporary stays have been granted in the past. *See Oral Proteolytic Enzymes; Withdrawal of Approval of New Drug Applications; Temporary Stay of Effective Date*, 50 FR 27492 (July 3, 1985) (issuing temporary stay “so that the drug sponsors have an opportunity to seek a judicial stay” and providing that temporary stay “will continue in effect until the court rules on the request for a stay”).

C. Statement of Grounds

1. Standard for Granting Stay

Petitioners are “interested persons” and thus have standing to seek a stay. 21 CFR §§ 10.3, 10.35(b). The standard for the Commissioner’s decision whether to issue a stay is as follows:

(e) The Commissioner shall promptly review a petition for stay of action. The Commissioner may grant or deny a petition, in whole or in part; and may grant such other relief or take such other action

as is warranted by the petition. The Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice. The Commissioner shall grant a stay in any proceeding if all of the following apply:

- (1) The petitioner will otherwise suffer irreparable injury.
- (2) The petitioner's case is not frivolous and is being pursued in good faith.
- (3) The petitioner has demonstrated sound public policy grounds supporting the stay.
- (4) The delay resulting from the stay is not outweighed by public health or other public interests.

21 C.F.R. § 10.35(e).

2. Reasons for Granting Stay

a. *Petitioners Will Suffer Irreparable Harm If a Stay Is Not Granted.*

The Order and Final Decision will result in irreparable harm to Petitioners. Petitioners are comprised of veterinarians who treat chickens and turkeys. The veterinarians' oath taken by Petitioners' members requires them to use their knowledge for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge. Part of that effort is assisting in the production of adequate wholesome food for the human population with a minimum of environmental damage.

(1) **There Is No Viable Alternative to Enrofloxacin.**

Enrofloxacin is extremely effective for treating the diseases for which it was approved in both chickens and turkeys under the specified conditions of use, and there are presently no viable alternatives to enrofloxacin and no new alternatives are anticipated in the near future. While other drugs are on the market, they are unsatisfactory for a number of reasons.

First, enrofloxacin is used infrequently and is most often used at the lowest authorized usage for only a few days. It is not an ongoing long-term treatment, and indeed one of its major advantages is that it is highly effective in a minimal amount of time. Alternative drugs such as tetracyclines, on the other hand, are much less effective because the targeted organisms have already developed some resistance, requiring higher doses of the drug to be administered for a longer time (thus further increasing resistance).

Second, one of the conditions of approval for enrofloxacin is that it may be used only as prescribed by a veterinarian under specified conditions, whereas tetracyclines have been used for decades in the U.S. poultry industry, without prescription requirements, to the point where tetracycline resistance is the norm, not the exception. Notably, enrofloxacin is used only in cases of serious high-mortality situations that threaten a large portion of a flock of chickens or turkeys. Enrofloxacin is not a drug that is used for routine treatment, and it is not administered when only a few birds are sick. The vast majority of birds are actually never treated with enrofloxacin.

Third, sulfa drugs, which are another potential alternative to enrofloxacin, are now used only sparingly because there are serious concerns about sulfa residues in poultry meat and other poultry products. Because respiratory diseases usually occur in the late stages of the production cycle, particularly in the case of chickens, the use of sulfa drugs poses a serious risk of product residues. Poultry companies view this risk as being too high because it jeopardizes product quality, and accordingly sulfa drugs are not a viable alternative to enrofloxacin.

Thus, if the Final Decision takes effect and enrofloxacin is withdrawn from the market, chicken and turkey health will suffer, and unhealthy turkeys lead to increased amounts of enteric pathogens entering the human food chain. In addition, Petitioners will suffer irreparable harm

because their members will not be able to treat chickens and turkeys in a way that is effective to protect the health of both the birds and the human beings who will later consume those birds.

(2) Immediate Implementation of the Final Decision Will Result in Severe Incompensable Economic Harm.

The Final Decision sets September 12, 2005, as the effective date of the withdrawal of enrofloxacin from the market. On that date, absent a stay, chicken and turkey producers will no longer be able to use enrofloxacin that they have already purchased. However, the diseases for which enrofloxacin is prescribed are seasonal in nature with peak occurrence being in the fall and winter—that is, in the months immediately subsequent to the effective date of the Final Decision. Many chicken and turkey producers have already planned for the upcoming season by purchasing supplies of enrofloxacin should their flocks suffer from disease. If enrofloxacin is withdrawn from the market on September 12 as scheduled, not only will chicken and turkey producers be faced with the need to use ineffective alternate treatments with minimal time to determine how to proceed, but they may also suffer greatly increased mortality in their flocks depending on the availability of such treatments and on the degree of ineffectiveness. Such increased mortality constitutes irreparable harm and may well put many smaller producers out of business.

(3) Immediate Implementation of the Final Decision and Order Will Have a Chilling Effect on the Willingness of Companies to Develop New Drugs for the Poultry Industry, Presenting Long-Term Harm to Poultry Production and Consumers.

The Final Decision orders the withdrawal of enrofloxacin based on so-called “new” evidence, notwithstanding that the FDA was fully aware of, and evaluated at the time of approval of the NADA, all of the potential effects of antibiotic use in veterinary medicine generally as well as those specifically related to the use of enrofloxacin in poultry. Final Decision at 91.

Also, the Final Decision concludes that the Respondent-Participants have not shown that enrofloxacin is “safe,” notwithstanding that the Final Decision does not provide any criteria for determining what is “safe” in the context of naturally-occurring bacteria. Because of these actions and the resulting uncertainty about the FDA’s standards for approving, and maintaining approval for, antibiotics, the Final Decision can legitimately be viewed as an arbitrary action by the FDA, and Petitioners have reason to believe that manufacturers of new animal drugs will be reluctant to invest the millions of dollars and other resources needed to find, develop, and obtain approval for new animal drugs. In the Animal Drug Availability Act, Congress recognized the need to promote the development of new animal drugs, yet the FDA’s withdrawal of approval for enrofloxacin could well act as a disincentive for the development of new animal drugs for poultry.

b. *Judicial Review of the Final Decision Would Not Be Frivolous and Would Be Pursued in Good Faith.*

It has never been suggested by anyone—CVM, the Administrative Law Judge, or the Commissioner—that such important scientific and legal issues as have been presented in the Enrofloxacin for Poultry case are frivolous. The Final Decision is precedent-setting because, notwithstanding that the debate about the use of antibiotics in veterinary medicine has been ongoing for over forty years, the withdrawal of enrofloxacin represents the first time an antibiotic used *solely* for therapeutic purposes has been ordered withdrawn due to concerns about antibiotic resistance. The Final Decision is also precedent-setting because the FDA has withdrawn the *only* truly effective antibiotic for the indicated uses, yet the FDA has still not defined what “safety” means in the context of a bacterium naturally present in the food chain.

The participants in the hearing—the trade association for the animal health industry and the holder of the NADA—responded to the Center for Veterinary Medicine’s Notice of

Opportunity for Hearing (NOOH) with facts, information, and analysis sufficient to be granted a hearing in this matter. Numerous other affected persons representing veterinary medicine, poultry producers, and other affected interests submitted voluminous evidence supporting the granting of a hearing in response to the NOOH. CVM submitted testimony from 35 witnesses and Respondent-Participants submitted testimony from 27 witnesses. An oral hearing for the purposes of cross-examination of witnesses was held from April 28 through May 7, 2003. CVM and Respondent-Participants submitted extensive post-hearing briefs. Respondent-Participants raised substantial factual legal and factual issues, including whether CVM had met its initial burden such that the burden shifted to Respondent-Participants to show that enrofloxacin is safe. The Administrative Law Judge's March 16, 2004, opinion was 68 pages long and the Final Decision is 126 pages long. As the extensive record in this matter shows, the underlying scientific and legal questions are not frivolous, and the potential consequences for poultry production are very serious.

The possible judicial review of a precedent-setting case is significant and not frivolous. While all the potential issues for judicial review may not yet have been examined by the parties to the proceeding, there at least several legal issues for the courts to review *de novo* that may result in a decision contrary to the FDA's interpretation of the law. For example, Respondent-Participants could seek judicial review of the FDA's exclusion of evidence of human health benefits based on the FDA's finding that the Supreme Court has, *by implication*, overruled the D.C. Circuit's holdings in *Hess & Clark v. FDA*, 495 F.2d 975 (D.C. Cir. 1974), and *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750 (D.C. Cir. 1980). Final Decision at 100-03. The decision to exclude such evidence largely underpins the FDA's evaluation of whether CVM met its initial burden of production and whether Respondent-Participants met their burden to prove that

enrofloxacin is safe. Final Decision at 93–100, 120. The legal question as to whether to weigh human health benefits as part of the determination of “safety” is not frivolous, especially since CVM conceded this requirement and the Administrative Law Judge so held. Despite this concession and holding, the Final Decision finds human health benefits irrelevant. Final Decision at 100, 120.

Two other examples of issues for judicial review are the FDA’s determination that evidence may be “taken as a whole” instead of evaluated on an individual basis to assess its reliability (Final Decision at 16) and the FDA’s interpretation of what constitutes “new evidence” (Final Decision at 85–90). These findings, among others, represent the critical pillars of the Final Decision, including the FDA’s determination that the initial burden had shifted from CVM to Respondent-Participants. A successful appeal on these and similar issues could well affect the decision about whether to withdraw the NADA, notwithstanding that the FDA has stated that it has evaluated, and not found reliable, the evidence that it excluded as irrelevant. These issues are clearly substantial and not frivolous, especially in the context of such a precedent-setting case.

Moreover, any potential pursuit of judicial review would be based on a good-faith belief that the Final Decision is wrong. To cite but one example noted above, the Final Decision’s finding that the Supreme Court has overruled the D.C. Circuit’s construction of the FDCA (Final Decision at 100–03) is subject to judicial review in good faith because the Supreme Court opinions cited in the Final Decision do not involve the FDCA. The courts are the best forum in which to decide that issue.

c. *Sound Public Policy Supports This Request for a Stay.*

Sound public policy considerations support this request for a stay. First, the Commissioner rejected Respondent-Participants’ contention that the evaluation of whether

enrofloxacin is “shown to be safe” requires an assessment of the human health benefits of enrofloxacin use. Petitioners believe that the D.C. Circuit will reverse the Final Decision on this point, necessitating a re-review of the matter. Sound public policy dictates that this issue should be definitively resolved by the courts before an order premised on a disputed standard for evaluating safety becomes effective.

Likewise, as noted above, the Final Decision concludes that the Supreme Court has overruled the D.C. Circuit’s construction of the FDCA and makes reference to Supreme Court opinions construing the Clean Air Act and the Occupational Safety and Health Act. (Final Decision at 100–03) The opinions in question analyze the meanings of particular words *within the contexts of those particular statutes*. The D.C. Circuit’s opinions analyzed the meaning of the word “safe” *within the context of the FDCA*, a wholly separate question. Petitioners believe that the Final Decision erroneously attempts to ascribe the context of two completely different statutes to the FDCA. Moreover, Petitioners respectfully submit that it is for the D.C. Circuit or the Supreme Court, not the FDA Commissioner, to determine whether the D.C. Circuit precedent remains binding, as the Commissioner lacks the authority to overrule either court. The public interest lies with having the courts determine whether the D.C. Circuit precedent in question has been overruled, because, if the courts decide that the Supreme Court has not overruled the D.C. Circuit’s construction of the FDCA, the Final Decision would be premised on error.

Finally, as discussed below, the Final Decision notes that, while selection for fluoroquinolone-resistant *Campylobacter* associated with the use of enrofloxacin is a greater risk than was originally anticipated in 1996 when the FDA approved such use, the actual incidence of *Campylobacter* infections in the United States has decreased in recent years. (Final Decision at 91) However, it is also clear from the evidentiary record that enrofloxacin is a uniquely effective

treatment for *E. coli*-induced air sacculitis, that without such treatment the incidence of fecal contamination of processed poultry increases and leads to increased microbial contamination of the poultry that is sold to consumers, and that, as a result, enrofloxacin has the overall effect of reducing foodborne illness, even if it is associated with increased risk in one particular area. In light of these facts, public policy supports granting a stay until the courts have determined whether the Administrative Law Judge and the Commissioner should have considered the very real human health benefits of enrofloxacin use and whether those benefits outweigh any risks.

d. *The Delay Resulting from the Stay Will Not Be Outweighed by Public Health or Other Public Interests.*

This matter has been pending for five years, during which period enrofloxacin has remained on the market. That fact alone is a telling reason why the entry of a stay is appropriate here, as the Final Decision contains no finding that the ultimate public health risks ascribed to enrofloxacin have increased during that time period or have become more imminent. Indeed, the Final Decision notes that the incidence of domestically-acquired *Campylobacter* infections has *decreased* in recent years. Final Decision at 119. The Initial Decision found that fluoroquinolone-resistant *Campylobacter* infections in humans “have the *potential* to adversely affect human health.” Final Decision at 5 (emphasis supplied), quoting Initial Decision at 66–67. In other words, both decisions find that while the use of enrofloxacin under the approved conditions of use in chicken and turkey results in selection for fluoroquinolone-resistant *Campylobacter*, it is by no means clear that such use is resulting in, or is even likely to result in, an actual or imminent threat to human health.

Moreover, it is undisputed that the FDA was aware of the potential for selection for fluoroquinolone-resistant *Campylobacter* when it approved the use of enrofloxacin in chicken and turkey. Final Decision at 91. The FDA authorized the use of enrofloxacin notwithstanding

that potential. The Final Decision finds that the risk is greater than CVM originally believed and that the restrictions on use anticipated at the time of approval are insufficient to counter the risk. *Id.* Yet given that the Final Decision notes that the actual incidence of infections from such resistant *Campylobacter* has decreased, the logical conclusion is that the greater *risk* does not necessarily correlate to greater *harm*. In view of these facts, it cannot be said that the continued sale and use of enrofloxacin suddenly poses an unacceptable public health risk as of September 12, 2005, when such sale and use has been deemed appropriate for the preceding five years. Put differently, it makes no sense to find that a few more months' delay is so imminent a public health risk that enrofloxacin must be pulled off the market immediately even though it remained on the market during the first five years of the pendency of this matter.

Respectfully submitted,



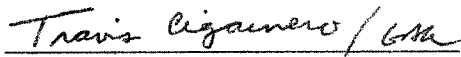
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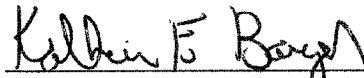
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CERTIFICATE OF SERVICE

I hereby certify that an original and four copies of the foregoing Petition for Stay of Action was hand-delivered this 26th day of August, 2005, to:

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