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June 13, 2006

Division of Drug Management
Food and Drug Administration
5630 Fishers Lane
Room 1061 (HFA-305)
Rockville, MD 20852

CITIZEN PETITION

Bayer HealthCare, Animal Health Division ("Bayer") submits this petition under Section 512 of the Federal Food, Drug, and Cosmetic Act ("FDCA") and 21 C.F.R. § 10.30. The petition asks that the Commissioner of Food and Drugs (the "Commissioner") refrain from approving all abbreviated applications for copies of Bayer's Baytril 100 Injectable Solution ("Baytril"), the subject of New Animal Drug Application ("NADA") No.141-068. Bayer's Baytril product label is protected by two patents covering dosing regimes, one of which is in effect until 2015 and claims methods for the treatment of bacterial infections by the administration of a single high dose. Bayer submits that any generic approved for a multiple dosing regime, which is losing patent protection this year, will be promoted and used extralabel for the protected single high dose regime. This would directly conflict with express provisions of the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) as well as FDA regulations, and would undermine the incentives for discovery and innovation that GADPTRA and patent laws were designed to protect.

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A. ACTION REQUESTED

Bayer respectfully requests that the Commissioner refrain from approving all abbreviated applications for generic enrofloxacin that purport to copy Bayer's Baytril 100 Injectable Solution, under sections 512 (d) and (n) of the FDCA. FDA has the authority to refuse to approve an application where the conditions for use are not likely to be followed in practice, and the responsibility to do so where the likelihood of patent rights being violated through extralabel usage is high.

B. STATEMENT OF GROUNDS

1. BACKGROUND

A. Bayer's NADA

Bayer holds an NADA for a fluoroquinolone product, enrofloxacin, that is sold under the trade name Baytril® 100 Injectable Solution (Baytril). Baytril is approved for administration in two distinct dosing regimens: a Single-Dose Therapy and a Multiple-Day Therapy. It is approved for use by prescription only in cattle, and only for the treatment of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *haemophilus somnus*. In addition, because of FDA's concerns regarding fluoroquinolone animal drug products and their potential safety risks from food-borne diseases, extralabel use, including a dosing regimen not appearing on the label, of enrofloxacin is prohibited in food-producing animals. 21 C.F.R. §522.812(d)((2)(iii).

Accordingly, the Baytril label states in pertinent part:

> **DOSAGE ADMINISTRATION:**
>
> Baytril® 100 injectable solution provides flexible dosages and durations of therapy. Baytril® 100 may be administered as a single dose for one day or for multiple days of therapy. Selection of the appropriate dose and duration of therapy should be based on an assessment of the severity of disease, pathogen susceptibility and clinical response. Administered dose volume should not exceed 20 mL per injection site.
>
> **Single-Dose Therapy:** Administer once, a subcutaneous dose of 7.5 - 12.5 mg/kg of body weight (3.4 - 5.7 mL/100 lb).
>
> **Multiple-Day Therapy:** Administer daily, a subcutaneous dose of 2.5 - 5.0 mg/kg of body weight (1.1 - 2.3 mL/100 lb). Treatment should be repeated at 24-hour intervals for three days. Additional treatments may be given on days 4 and 5 to animals which have shown clinical improvement but not total recovery.
>
> * * * *
>
> **CAUTION:**
>
> Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.
>
> Federal (U.S.A.) law prohibits the extralabel use of this drug in food producing animals.

B. Bayer's Patented Discoveries

Baytril is the culmination of intensive research undertaken and funded by Bayer. As a result of that research, the United States Patent and Trademark Office awarded patents to Bayer, two of which are of particular relevance here: U.S. Patent No. 4,670,444 ("the '444 patent") and U.S. Patent No. 5,756,506 ("the '506 patent"). Both patents currently protect the Dosing Administration regimens for Bayer's Baytril 100 product.

The '444 patent discloses and claims, among other things, fluoroquinolone compounds and their use as antimicrobial agents. The patent, which expires on December 9, 2006, also covers the Multiple dosing therapy approved for Baytril 100.

The '506 patent discloses and claims, among other things, a process for treating bacterial infections using one high dose of a fluoroquinolone. Accordingly, the '506 patent, which expires on June 27, 2015, covers the Single-Dose therapy approved for Baytril. Bayer's discovery of the Single-Dose therapy was a breakthrough in antibacterial treatment. As pointed out in '506, the uniqueness of this patent is not based on a special formulation. The same formulation is administered whether the Multiple-Dose or Single-Dose regimen is used. The difference recognized by Bayer in seeking this patent was that fluoroquinolone compounds exhibit concentration-dependent antibacterial activity rather than time-dependent activity. Administering Baytril 100 as a Single-Dose regimen allows veterinarians to vastly reduce the time and expense associated with the treatment of infected animals. Whereas the Multiple-Day dosing therapy can require the daily administration of antibacterial for up to five days, the Single-Dose therapy requires only one administration.

Bayer has supported studies demonstrating that drug plasma concentrations, which are achievable with single high dose therapy, are adequate to kill spontaneously occurring fluoroquinilone resistant mutants. This supports the American Veterinary Medical Association's position statement that encourages uses of animal antimicrobials to maximize the therapeutic effect while minimizing the chance of resistance development.

Bayer conducted extensive clinical field trials, over several years, to demonstrate that the Single-Dose regimen worked in the field, and also conducted follow up conformational studies to verify those original findings. In addition to the clinical trials, Bayer also conducted residue studies so that the Single-Dose regimen could be included on Baytril 100 label, once the product was approved. The '506 patent application was filed on May 27, 1997. Baytril 100 was approved by FDA on July 24, 1998.

C. Bayer's Post-Approval Efforts

Bayer also voluntarily established a Post-Approval Monitoring Program (PAMP) for Baytril to help FDA determine if administration of enrofloxacin to cattle alters the minimum inhibitory concentrations (MICs) of resident gastrointestinal *E. coli* and *Salmonella spp.* to enrofloxacin. FDA formally accepted the company's proposals in August of 1998, and Bayer operated under this program until February 2, 2001 when FDA communicated that the data collected was sufficient and the PAMP was no longer necessary.

The PAMP consisted of various monitoring activities including data collection to help detect MIC shifts based upon mutant selection following administration of enrofloxacin. Bayer has also instituted and maintained a unique distribution system designed to manage and record the product distribution in the market, thereby maintaining control of the product until it is sold to the veterinarian. Bayer developed and regularly updates its internal training programs specific to this issue, in order to educate its sales force on the judicious use principles of antimicrobials. Bayer also

established and has continued external education programs to similarly train veterinarians, sales agents, distributors and producers. Finally, Bayer continued its efforts to research the prudent and correct use of the product, to assure it stays abreast of the issues.

D. Baytril Is Principally Used In A Single-Dose Therapy

Recent independent research of 300 range and feedlot veterinarians administering and/or prescribing Baytril 100 was conducted by Doane Marketing Research. [See Tab A] Classes of cattle treated by the veterinarians surveyed included cattle on feed, stocker/feeders and beef cows, calves and replacement heifers. Results of this research determined that 72%-76% of the animals treated with Baytril 100, for bovine respiratory disease, received a high Single-Dose, while only 24%-28% received a Multiple-Day low dose.

It is reasonable to conclude that any generic approved for the Multiple-Day dosing regimen would likely be used as a Single-Dose. In fact, independent veterinarians in the industry further support this conclusion, recognizing that with the Single-Dose use compliance improves and as a result efficacy may improve. We attach three affidavits of experienced practicing veterinarians that confirm that there are significant advantages to the single dose therapy, and, as a result, there is no question that there will be consistent off-label use of an approved generic multi-day enrofloxacin product. [See Tab B]

2. ARGUMENT

The Commissioner should refrain from approving an abbreviated application for a drug copy of Baytril limited to a Multiple-Day dosing therapy regime (with no mention of a Single-Dose therapy regime) because doing so would contravene the clear language of GADPTRA, which prohibits approval of an abbreviated application under the present circumstances.

GADPTRA expressly provides that "the Secretary shall approve an abbreviated application for a drug unless the Secretary finds . . . the conditions of use proscribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice . . ." 21 U.S.C. § 360b(c)(2)(A)(ii), emphasis added. As discussed above, it is reasonably certain that an abbreviated application label limited to the Multiple-Day dosing therapy regimen would not be followed in practice. The independent Market Research cited above provides compelling evidence that a generic Baytril drug product is likely to be used in an extralabel Single-Dose therapy regimen. This alone is enough to deny approval.

In addition, granting abbreviated approvals under the present circumstances would also undermine the delicate balance between rewarding innovation and encouraging low cost drugs that GADPTRA was intended to strike. Approval would ignore Bayer's rightful reward for the effort and expense it has invested in the discovery

of the Single-Dose therapy regimen, and it would reward generics for encouraging extralabel use of an important antibiotic that FDA has long sought to control. [1]

It is contrary to public policy and the letter and spirit of GADPTRA for FDA to evade its responsibility to police abbreviated approvals of important antibiotics and force Bayer to endure the added expense of privately enforcing its patent rights to stop extralabel use.

The circumstances of the present request are substantially different than those presented in earlier cases involving extralabel uses of human drugs, such as Bristol-Myers Squibb Co. v. Shalala, 91 F.3d 1493 (D.C. Cir. 1996) and Sigma-Tau Pharmaceuticals, Inc. v. Schwetz, 2001 U.S.Dist. LEXIS 11247 (D.Md, Aug. 3, 2001). Neither of those cases involved the agency's approval of a drug for animal use. Consequently, neither involved an application of GADPTRA or regulations promulgated pursuant to it. The dispute in Bristol-Myers focused on the narrow question of whether 21 U.S.C. § 355(j)(2)(A)(v), a provision applying to human drugs, requires a generic label to be "the same" as that of a pioneer. Similarly, the Sigma-Tau court only addressed specific provisions of the Orphan Drug Act, 21 U.S.C. §§ 360aa-ee, which was implemented to provide drug manufacturers with incentive to develop drugs for the

[1] FDA regulations prohibit the extralabel use of fluoroquinolones, like enrofloxacin, in food-producing animals. FDA specifically restricted such extralabel uses of fluoroquinolones nearly a decade ago. 62 Fed. Reg. 27944 (May 22, 1997), codified at 21 C.F.R. § 530.41(a)(10). In addition, a similar regulation specifically prohibits the extralabel use of enrofloxacin in food-producing animals (21 C.F.R. §522.812(d)(2)(iii)) and in 1988, FDA published an update advising the industry about the prohibition against extralabel use of Baytril. CVM Update, Extra-Label Use of Baytril 100 Prohibited, Including Use in Dairy Cattle or Veal Calves, September 22, 1998.

treatment of rare diseases or disorders affecting small patient populations. Neither provision is implicated by Bayer's request.

In passing GADPTRA, Congress recognized that "[t]he purpose of the bill is to create in the animal drug industry similar conditions for generic drugs and patent term restoration as Congress did in the human drug industry in 1984 ... *except in those respects where animal drugs must be treated differently.* For example, Title I of this bill requires additional scientific testing when necessary to assure food safety in the case of animal drugs given to food-producing animals." House Report No. 100-972(1998) (emphasis added). Congress thus explicitly contemplated situations where there will be decisions made by FDA in the animal drug approval context that will not be consistent with decisions made on the same issue in the human drug approval context.

Moreover, there is little guarantee that any other company would go to the expense that Bayer has to develop rigorous data collection and evaluation, and establish a controlled distribution system and focused education and training program throughout the distribution chain. Bayer also committed to providing FDA with biannual reports including information regarding the monitoring program and drug distribution by state. Bayer continues to provide FDA with drug distribution data on a state-by-state basis.

FDA can not trust that other companies will be as dedicated as Bayer has been to implementing such a program and monitoring use of Baytril in the field. In light of the concerns FDA has about this category of product, it is essential that this be a part of the

consideration of any approval for generic enrofloxacin. Particularly, FDA, at a minimum, must be ready to make generic approval contingent upon the establishment of the same type of post approval program as implemented by Bayer, with stringent controls on distribution so that the data collected is meaningful and neither duplicative or incomplete.

Finally, approval of a generic for only a Multi-Day dosing regimen could undermine FDA's ability to control, monitor and regulate extralabel use, an express concern and prohibition of FDA's as it approves animal drugs in general, and specifically with respect to this class of animal drugs, as discussed above. The introduction of a Multi-Day generic will lead to a certain expectation of extralabel uses and infringement of Bayer's '506 patent covering the Single-Dose therapy regimen. As a result, veterinarians will arguably be knowingly contributing to the violation of GADPTRA and to patent infringement by not closely monitoring and documenting use of generic product.

3. CONCLUSION

In advance of granting any generic approval for enrofloxacin, FDA must consider the provisions and intent of GADPTRA as they apply to the present, somewhat unusual, circumstances. It is Bayer's position that such an evaluation can lead to only one reasonable conclusion: the disapproval of generic enrofloxacin.

C. ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 C.F.R. § 25.31.

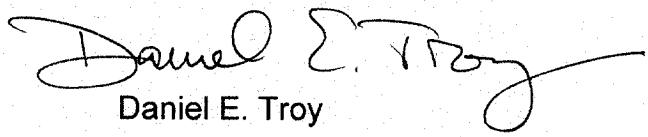
D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

E. 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.

Respectfully submitted,



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