UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

BAYER HEALTHCARE, LLC,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Civil Action No. 13-487 (RMC)**
	)	
	)	
UNITED STATES FOOD AND DRUG ADMINISTRATION, *et al.*,[1]	)	
	)	
	)	
Defendants.	)	
	)	

MEMORANDUM OPINION

Bayer HealthCare, LLC patented a highly-successful drug and method for treating bovine respiratory disease named Baytril® 100. While Baytril can be administered over three days, its real advantage is that it can also be administered in a single injection to cure the animal. In 2006, Bayer submitted a Citizen Petition to the Food and Drug Administration, expressing its concern that generic versions of Baytril could be labeled only for multi-day use but inevitably would be used in a single dose, contrary to its labeling. Bayer supported its Petition with affidavits and market research. Without addressing the Petition, FDA recently approved a generic version of Baytril® 100, called Enroflox 100, which is labeled only for multi-day administration. Bayer immediately filed suit, claiming that FDA's approval of Enroflox 100 violated the statutory command that FDA not approve an animal drug when it finds "the

[1] Defendants are United States Food and Drug Administration; Margaret A. Hamburg, in her official capacity as Commissioner; Center for Veterinary Medicine; Bernadette Dunham, in her official capacity as Director; United States Department of Health and Human Services; and Kathleen Sebelius, in her official capacity as Secretary. The Court refers to Defendants, collectively, as the Food and Drug Administration (FDA).

conditions of use prescribed, 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). FDA acknowledges that it erred by failing to respond to Bayer's Citizen Petition but nonetheless asks the Court to afford its decision to approve Enroflox 100 deference in light of the agency's expertise in veterinary medicine. The matter proceeded to a hearing on Bayer's motion for a temporary restraining order on April 12, 2013.

For reasons stated at the hearing and specified below, the Court issued a temporary restraining order. FDA offers no evidence that it considered any of the concerns, facts, or arguments raised in Bayer's Citizen Petition when it approved Enroflox 100—concerns which strongly suggest that approval of a generic for Baytril only for multi-day use might well violate 21 U.S.C. § 360b(c)(2)(A)(ii). It says only that it trusts veterinarians and ranchers to follow the Enroflox 100 labeling for multi-day use and an applicable regulation, despite the ready ease (and benefits) with which Enroflox 100 could be administered in a single dose contrary to its label. The Court concluded that Bayer is likely to succeed on the merits, would suffer irreparable harm, and is favored by the balance of equities. Also, the public interest supports a TRO. The Court ordered FDA to suspend its approval of Enroflox 100, as well as its approval of the label, for treating cattle (but not swine). The Court also ordered FDA to notify all interested parties of the Order. *See* Order [Dkt. 11]. This Memorandum Opinion explains its rationale. A hearing on Bayer's motion for a preliminary injunction is scheduled for April 25, 2013.

I. FACTS

A. Baytril® 100

Bayer HealthCare, LLC patented a drug and method for treating bovine respiratory disease (BRD) called Baytril® 100 (Baytril). Prior to Baytril, the "conventional wisdom was that BRD had to be treated by administering multiple, low doses of antibiotic – a time consuming, expensive, and cumbersome process." Compl. ¶ 19 [Dkt. 4]. Bayer "revolutionized the industry" by developing a single, high-dose treatment with a fluoroquinolone antibiotic. *Id.* ¶ 20.

Bayer secured two patents for Baytril— U.S. Patent No. 4,670,444 (the "444 patent") and U.S. Patent No. 5,756,506 (the "506 patent"). Mot. for Leave to File under Seal [Dkt. 1], Ex. 3 [Dkt. 1-5] ("Citizen Petition") at 3. Both patents protect the "Dosing Administration regimens" for Baytril. The 444 patent claims the compound itself, "fluoroquinolone compounds and their use as antimicrobial agents," *and* the multiple-dosing therapy. Citizen Petition at 4. The 506 patent claims the single, high-dose therapy using fluoroquinolone. *Id.*; *see also* Mot. for Leave to File Under Seal, Ex. 1 [Dkt. 1-3] ("506 patent"). The single, high-dose therapy "allows veterinarians to vastly reduce the time and expense associated with the treatment of infected animals." Citizen Petition at 4. Bayer commercialized Baytril for single, high-dose therapy in 1998. *Id.* at 5. The 444 patent expired on December 9, 2006. The 506 patent expires on June 27, 2015. *Id.* at 4.

Baytril comes as a "ready-to-use injectable antimicrobial solution." Mot. for Leave to File Under Seal, Ex. 2 [Dkt. 1-4] (Product Label for Baytril). The labeling for Baytril provides detailed instructions for administration:

> **Dosage and Administration**:
>
> Baytril® 100 provides flexible dosages and durations of therapy.
>
> Baytril® 100 may be administered as a single dose for one day (cattle and swine[2]) or for multiple days (cattle) 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.
>
> **Cattle:**
>
> **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 that have shown clinical improvement but not total recovery.

Id. The labeling also includes a list of animal weights and the corresponding recommended dosages. *Id.*

B. Citizen Petition

On June 13, 2006, Bayer filed Citizen Petition No. 2006P-0249 with the Food and Drug Administration (FDA), pursuant to 21 C.F.R. § 10.25(a) ("An interested person may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."). In the Petition, Bayer expressed its concern that any generic application based on Baytril intended for multiple-day therapy would be used in a single, high-dose regimen, contrary to its label. Citizen Petition at 7. In other words, after expiration of the 444 patent, drug companies could file an Abbreviated New Animal Drug

[2] Although Baytril is also approved for treatment of swine, Bayer's Complaint addresses only Baytril's treatment of BRD in cattle. *See generally* Compl. Accordingly, the Court's Order suspending FDA's approval of Enroflox 100 concerns only its approval and labeling for cattle, not swine. *See* Order [Dkt. 11].

Application (ANADA) to market a generic version of Baytril limited to multiple-day dosing. Bayer was concerned that the labeling for such a generic might direct multiple, low-dose administration but that veterinarians and/or ranchers would inevitably engage in off-label use of the product and administer it in a single, high-dose manner. *Id.*

To substantiate its claim that veterinarians would engage in off-label use, Bayer submitted independent market research and affidavits from three veterinarians. *See* Citizen Petition, Tabs A-D. Its market research determined that 72%-76% of animals treated with Baytril received a high single dose, while only 24%-28% received a low multiple-day dose. All three veterinarians cited the advantages of a single, high-dose treatment and concluded that off-label use of a generic was likely to occur. *See* Citizen Petition, Tab B (Decl. of K. Shawn Blood) ("There is no question in my mind that, due to labor, compliance and other economic pressures, an approved multi-day generic will be used off label use as the single high dose."); *id.*, Tab C (Decl. of Kelly F. Lechtenberg) ("I have no doubt there will be tremendous pressure in some organizations to use a less expensive generic off label as a high single dose."); *id.*, Tab D (Decl. of Steve Lewis) ("There is no question, that a generic multi-day enrofloxacin will be used extra-label as the protected single high dose regimen.").

Given its concern that off-label use would be inevitable, Bayer asked FDA to refrain from approving an application for a generic of Baytril limited to a multiple-day dosing therapy. The Federal Food, Drug, and Cosmetic Act (FFDCA) provides in part that "the Secretary shall approve an abbreviated application for a drug unless the Secretary finds . . . the conditions of use prescribed, 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). FDA regulations also prohibit the extra-label use of fluoroquinolones (including enrofloxacin, the active

ingredient in Baytril and Enroflox) in food-producing animals. *See* 21 C.F.R. § 530.41(a)(10); 21 C.F.R. § 522.812(d)(2) (regulating enrofloxacin). Bayer asserted that approval of a generic version of Baytril limited to a multiple-day dosing therapy would violate the FFDCA and "could undermine FDA's ability to control, monitor and regulate extralabel use." Citizen Petition at 10.

On December 8, 2006, FDA provided a "tentative response" to Bayer's Citizen Petition, noting that 21 C.F.R. § 10.30 requires a response to a citizen petition within 180 days. *See* Mot. for Leave to File under Seal, Ex. 6 [Dkt. 1-8] (FDA response). FDA stated that it was "currently considering the issues raised" by the Petition and that "the agency will require additional time to issue a final response because of the complexity and the number of issues raised in [the] petition." *Id.* In September 2009, Bayer contacted FDA regarding the status of its Petition and was told that the Petition was under active review. Mot. for Leave to File under Seal, Att. 1 [Dkt. 1-1] (Decl. of Alan R. Bennett) ¶ 6. Apart from its initial tentative response, FDA has not otherwise commented or responded to the Citizen Petition as of the date of the hearing on a TRO.

C. Procedural History

In 2008, Norbrook Laboratories, Limited submitted an ANADA to manufacture and sell a generic version of Baytril, Enroflox 100 (Enroflox), in a multiple-day dosing regimen. Compl. ¶ 24. On November 7, 2008, Bayer sued Norbrook for patent infringement in the Eastern District of Wisconsin. Notice of Filing [Dkt. 10], Att. 1 [Dkt. 10-1] (E.D. Wis. Complaint). That lawsuit was settled, and the court entered a stipulation of dismissal on March 22, 2012. *Id.*, Att. 2 [Dkt. 10-2] (Stipulation of Dismissal). On May 8, 2012, Norbrook informed FDA of the settlement and the court's dismissal of the case. *Id.*, Att. 3 [Dkt. 10-3] (Letter from Norbrook to FDA). In its letter, Norbrook also notified FDA that it was "authorized by Bayer to market and

sell the product that is the subject of [the ANADA] as of September 15, 2012." Directly after this statement, Norbrook acknowledged, "[o]f course, Norbrook's ability to enter the market on the Agreed Entry Date remains subject to FDA's prior approval of [the ANADA]." *Id.*

On March 29, 2013, FDA approved Norbrook's ANADA for Enroflox for administration as a single dose for one day in swine or for multiple days of therapy for cattle. Compl. ¶ 27; Notice of Filing, Att. 4 [Dkt. 10-4] (Product Label for Enroflox 100). Like Baytril, Enroflox also comes as a "ready-to-use injectable antimicrobial solution." Product Label for Enroflox 100. Enroflox's labeling for multiple-day therapy in cattle is identical to Baytril's for the same use and includes a table for recommended dosage based on animal weight. Specifically, the dose administration instructions on the label state: "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 that have shown clinical improvement but not total recovery." *Id.*

On April 10, 2013, Bayer filed the instant Complaint and a motion for a temporary restraining order and preliminary injunction. *See* Mot. for TRO [Dkt. 5]. Bayer asks the Court to vacate FDA's final approval of Norbrook's ANADA for Enroflox until this case is resolved.

II. LEGAL STANDARDS

A. Temporary Restraining Order

The standard that applies to preliminary injunctions also applies to temporary restraining orders. *Experience Works, Inc. v. Chao*, 267 F. Supp. 2d 93, 96 (D.D.C. 2003). A district court may grant a preliminary injunction "to preserve the relative positions of the parties until a trial on the merits can be held." *Univ. of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981).

An injunction is an equitable remedy so its issuance falls within the sound discretion of the district court. *See Hecht Co. v. Bowles*, 321 U.S. 321, 329 (1944). A plaintiff seeking a preliminary injunction must establish that:

> (a) he is likely to succeed on the merits;
>
> (b) he is likely to suffer irreparable harm in the absence of preliminary relief;
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> (c) the balance of equities tips in his favor; and
>
> (d) an injunction is in the public interest.

Winter v. NRDC, Inc., 555 U.S. 7, 20 (2008). The D.C. Circuit has further instructed that "the movant has the burden to show that all four factors . . . weigh in favor of the injunction." *Davis v. Pension Benefit Guar. Corp.*, 571 F.3d 1288, 1292 (D.C. Cir. 2009).

In the past, courts have balanced the four factors on a "sliding scale," *i.e.*, a lesser showing on one factor could be surmounted by a greater showing on another factor. *CSX Transp., Inc. v. Williams*, 406 F.3d 667, 671 (D.C. Cir. 2005). *Winter v. NRDC* called this approach into question: "[i]ssuing a preliminary injunction based only on a *possibility* of irreparable harm [despite finding a strong likelihood of success on the merits] is inconsistent with our characterization of injunctive relief as an extraordinary remedy that may only be awarded upon a clear showing that the plaintiff is entitled to such relief." *Winter*, 555 U.S. at 22. A positive showing on all four factors is required. *See Davis*, 571 F.3d at 1292.

B. Administrative Procedure Act

A reviewing court shall "hold unlawful and set aside agency action, findings, and conclusions found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A); *see Tourus Records, Inc. v. DEA*, 259 F.3d 731, 736 (D.C. Cir. 2001). The basic legal tenets here are longstanding and clear: A reviewing court

"must consider whether the [agency's] decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Marsh v. Or. Natural Res. Council*, 490 U.S. 360, 378 (1989) (internal quotation marks omitted). At a minimum, the agency must have considered relevant data and articulated an explanation establishing a "rational connection between the facts found and the choice made." *Bowen v. Am. Hosp. Ass'n*, 476 U.S. 610, 626 (1986) (internal quotation marks omitted); *see also Pub. Citizen, Inc. v. FAA*, 988 F.2d 186, 197 (D.C. Cir. 1993) ("The requirement that agency action not be arbitrary or capricious includes a requirement that the agency adequately explain its result."). An agency action is arbitrary or capricious

> if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). "The scope of review under the 'arbitrary and capricious' standard is narrow and a court is not to substitute its judgment for that of the agency." *Id*. Rather, agency action is normally "entitled to a presumption of regularity." *Citizens to Pres. Overton Park, Inc. v. Volpe*, 401 U.S. 402, 415 (1971), *abrogated on other grounds by Califano v. Sanders*, 430 U.S. 99 (1977).

III. ANALYSIS

A. Likelihood of Success on the Merits

Bayer asserts that FDA acted arbitrarily and capriciously when it approved Norbrook's ANADA. Bayer argues that approval of the ANADA "evinces a failure to consider a crucial aspect of the problem" and runs counter to the evidence before the agency on the critical issue of the generic's potential for off-label use in a single, high dose. Sealed Doc. [Dkt. 2] (Pl.

Mem. in Support of its Mot. for TRO (Pl. Mem.)) at 12. Bayer also argues that FDA's approval of Norbrook's ANADA was arbitrary and capricious because it failed to provide *any* explanation for its action.

FDA responds that its decision was reasonable in light of the record before it at the time of the decision. FDA points to Norbrook's letter, advising that Bayer and Norbrook had settled the patent lawsuit.[3] It points also to the label for Enroflox, which specifies that when used for cattle, the drug is only for multiple-day therapy and includes a warning that federal law "prohibits extra-label use of" the drug. *See* Product Label for Enrofox 100. FDA also asserts that it made a reasonable decision based on its years of expertise in veterinary drugs. FDA recognizes that it erred by failing to respond to Bayer's Citizen Petition before approving Enroflox but argues that the Court cannot conclude that FDA "knew" when making its decision that off-label use was reasonably certain to occur. The Court rejects FDA's formulation of the issue: resolution does not turn here on what FDA "knew" in a vacuum, but whether, based on all the facts before it, FDA *had found* that the conditions of use specified in the proposed labeling were not reasonably certain to be followed in practice. *See* 21 U.S.C. § 360b(c)(2)(A)(ii). Since FDA offers no evidence that it considered the full record before it or made the necessary finding, FDA presents an exceptionally weak position despite the excellence of its lawyering.

On this record, it is clear that FDA had before it a directly-applicable Citizen Petition supported by sworn evidence that a label for a Baytril generic approved only for multiple-day dosing was not reasonably certain to be followed in practice. Notably, although aware of Bayer's Citizen Petition, Norbrook never filed any response refuting the facts asserted in the Petition. *See* Compl. ¶ 24. The facts set forth in the Petition stand unchallenged and bereft

[3] The settlement agreement is not in evidence, and the Court concluded that nothing in the parties' arguments at the hearing precluded Bayer's claims under the APA against FDA here.

of reasoned agency response. Although counsel for FDA claimed that someone within FDA had prepared a tentative draft response denying the Citizen Petition, Hr'g on Mot. for TRO at 30:13-16, neither a "tentative draft" nor the prediction that a response is forthcoming can substitute for reasoned decisionmaking at the time FDA approved the Norbrook application for Enroflox.

At this juncture, FDA presents only legal argument that the Court should presume regularity and defer to its expertise. But, while agency action may generally be "entitled to a presumption of regularity," *Volpe*, 401 U.S. at 415, here FDA itself acknowledges that its action has not been regular: it failed to respond to the Citizen Petition for years and failed to provide a reasoned basis for rejecting it before approving Enfrolox. *See* Hr'g on Mot. for TRO at 30:25 – 31:1-2 ("[The agency] definitely got mud on its face for not having decided the petition prior to or at the time it approved the ANADA."). Further, the present record is devoid of any explanation *at all* for the basis for FDA's decision to approve Enroflox.

Bayer's concern for off-label use of a generic to Baytril cannot be said to be unreasonable or illogical. The labels for both drugs are very similar and the instructions on Enroflox's label are identical to Baytril's instructions for multiple-day therapy in cattle. Enroflox, like Baytril, is sold as a "ready-to-use injectable antimicrobial solution," and the table of recommended dosages dependent on animal weight demonstrates that veterinarians (and/or ranchers) have flexibility to adjust the dose volume. *See* Product Label for Enroflox 100. Bayer makes the commonsensical argument that when administering the very same drug as Baytril, given the many advantages of Baytril's single, high-dose administration well known to veterinarians and ranchers, users are reasonably certain to use a single high dose off-label in lieu of the multiple-day therapy specified on the label.

The present record strongly suggests that FDA "entirely failed to consider an important aspect of the problem." *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43. The Court cannot find that FDA engaged in reasoned decisionmaking as the APA requires. *See Bowen*, 476 U.S. at 626 (requiring a "rational connection between the facts found and the choice made" (internal quotation marks omitted)). The Court thus concluded that, on this record, Bayer is likely to prevail on the merits of its claim that FDA acted arbitrarily and capriciously when approving the ANADA for Enroflox.

B. Irreparable Harm

As its basis for irreparable harm, Bayer points to the effect on its market share, arguing that the launch of Norbrook's generic "will change the market irreversibly if not reversed by the requested interlocutory relief." Pl. Mem. at 18. Without the requested relief, Bayer states it "will be irreparably harmed by, *inter alia*, the further price erosion, deep drops in revenues, loss of valuable customer relationships, loss of research and development funds, and fewer revenue-generating future products in the pipeline." *Id.* Bayer includes a declaration from Cary R. Christensen, the senior director of the Food Animal Products business unit of Bayer's Animal Health Division, to support its claims of irreparable harm. Sealed Doc., Att. 1 [Dkt. 2-1] (Decl. of Cary R. Christensen). Mr. Christensen explains in detail how Norbrook's generic will erode the price of Baytril and affect its market share, as well as the effect Norbrook's generic will have on Bayer's business. *Id.* FDA counters that Bayer has not made a showing that its financial loss will be "irreparable" and asserts that the magnitude of the harm to Bayer caused by FDA's decision cannot be determined based on the content of Mr. Christensen's declaration because it fails to provide a full context for his assertions.

Courts have recognized that price erosion and diminished market share can constitute irreparable harm. *See, e.g.*, *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm); *Polymer Technologies, Inc. v. Bridwell*, 103 F.3d 970, 975-76 (Fed. Cir. 1996) (explaining how loss of market opportunities constitutes evidence of irreparable harm); *Bio-Technology Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1566 (Fed. Cir. 1996) (loss of revenue, goodwill, and research and development constitute irreparable harm). Once a less expensive version of a drug enters the market, the original drug manufacturer cannot maintain its initial price and stands to lose good will among its customers when a less expensive drug with the same efficacy becomes available. Indeed, Mr. Christensen explains specifically how Bayer will experience a decline in market share, price erosion, loss of customer good will, and loss of research and development funding as a result of Enroflox's entry into the market. Christensen Decl. ¶¶ 26, 31, 35. The Court concludes on this record that Bayer is likely to suffer irreparable harm if Enroflox remains in the market for treating BRD in cattle pending resolution of this litigation.

C. Balance of Equities

Bayer contends that no harm will come to FDA from a TRO that maintains the prior status quo pending a resolution of this dispute on the merits. Bayer also argues that Norbrook had years to respond to Bayer's Citizen Petition and failed to do so and that Norbrook waited years to market its generic. Therefore, it concludes, waiting only "slightly longer" for resolution of this dispute will not result in substantial injury to Norbrook. Pl. Mem. at 23. FDA responds that it has an interest in having its decision to approve the application for Enroflox

upheld and that Norbrook, having complied with all the statutory requirements for applying for approval of a generic, also has an interest in having the approval of its application upheld.

The Court appreciates FDA's institutional interest but, given its long-standing disregard of Bayer's Citizen Petition, its argument has a hollow center. Bayer and Norbrook have contrasting commercial interests in the outcome of this litigation. However, Bayer attempted to obtain a more timely resolution of these issues through its Citizen Petition, to which Norbrook raised no objection, and, in any event, Bayer could reasonably anticipate that FDA would follow the strictures of the statutory command that it consider whether the specifications of the label "are not reasonably certain to be followed in practice." 21 U.S.C. § 360b(c)(2)(A)(ii). There is no evidence that FDA complied with the statutory mandate, and the record and common sense suggest that off-label use could readily occur. While Norbrook has been anticipating and preparing to market Enroflox, it has not proceeded far into the market since its very recent FDA approval. On this record, the harm to Bayer outweighs any harm to FDA or Norbrook while the Court considers the motion for a preliminary injunction.

D. The Public Interest

The public has an interest in federal agency compliance with its governing statute. Here, FDA has shown no attention to the congressional mandate that it withhold approval of a drug for animals when it finds that "the conditions of use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice." *Id.* FDA had a factual record before it immediately on point but appears to have ignored those facts. At a minimum, it is clear from the present record that FDA did not address the full record or make a reasoned decision regarding whether Enroflox's directive only for multiple-day therapy was not reasonably certain to be followed in practice, in light of the many well-known advantages to

single, high-dose therapy. The public interest is best served by ensuring compliance with the statute.

IV. CONCLUSION

For the reasons stated, the Court granted in part and denied in part Plaintiff's Motion for a Temporary Restraining Order [Dkt. 5] on April 12, 2013.

Date: April 17, 2013

/s/
ROSEMARY M. COLLYER
United States District Judge