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VIA HAND DELIVERY

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

Re: Bayer HealthCare's Citizen Petition, Docket No. FDA-2006-P-0010 (formerly 2006P-0249)

Bayer HealthCare LLC, Animal Health Division ("Bayer") respectfully submits this supplement to Citizen Petition No. FDA-2006-P-0010, filed June 13, 2006, in connection with the review of the petition by the Commissioner of the Food and Drug Administration ("FDA").

I. FDA's Statutory Mandate

Bayer's Citizen Petition requests that FDA refrain from approving a generic version of Bayer's Baytril® 100 product pursuant to Section 512 of the Food, Drug, and Cosmetics Act (codified at 21 U.S.C. § 360b). The Act prohibits approval of an abbreviated new animal drug application if 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). This statutory language is clear—FDA is prohibited from approving a generic application if the drug product is not reasonably certain to be used according to its labeling in practice.

The statute is unambiguous and permits no other interpretation. Indeed, this interpretation was adopted explicitly by FDA and the Court in the lawsuit challenging the

approval of an application by Norbrook Laboratories, Ltd. ("Norbrook") to market a generic version of Baytril®:

> THE COURT: ...If they're not reasonably certain to be followed in real practice, then the Secretary shall not approve the ANADA application.
>
> MR. KELL[1]: That's correct.
>
> THE COURT: That's the way it works.

See Ex. 1, *Bayer v. FDA*, Transcript at 30:3–7; *see also id.* at 61:7–14 (the Court identifying the issue as "...whether or not the Secretary fulfilled the clearly written in English obligation in the Food and Drug Cosmetic Act" to not approve an abbreviated application for a drug unless the Secretary finds the conditions of use in the proposed labeling are reasonably certain to be followed in practice); *id.* at 27:21–28:13 (Court and FDA agreeing that the issue under the statute is whether end-users will administer the product according to the label or not). In cases where the drug product of the abbreviated application is not reasonably certain to be used according to its label, the statutory prohibition on approval under § 360b(c)(2)(A)(ii) is plain, direct, and unconditional.

This unconditional prohibition based on the likelihood of off-label use alone distinguishes the consideration of *abbreviated* applications under subsection (c)(2)(A) from *full* new animal drug applications under other sections of the code. For instance, § 360b(d) sets forth additional bases for rejecting any new animal drug application, and subsection (2)(D) of that

[1] Counsel for FDA, its Commissioner, Center for Veterinary Medicine, its Director, US Department of Health and Human Services, and its Secretary. *See Bayer v. FDA et al.*, Civil Action No. 13-487 (D.D.C. 2013) (RMC).

provision explicitly links consideration of the label to safety concerns. Subsection (c)(2)(A) at issue here, which relates only to abbreviated new animal drug applications, does not. *Compare* 21 U.S.C. § 360b(c)(2)(A)(ii) ("[T]he 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") *with* 21 U.S.C. § 360b(d)(2)(D) ("In determining whether such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, the Secretary shall consider, among other relevant factors . . . whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice.") "We normally presume that, where words differ as they differ here, Congress acts intentionally and purposely in the disparate inclusion or exclusion." *Burlington Northern & Santa Fe Ry. v. White*, 548 U.S. 53, 62–63 (2006) (internal quotation and citation omitted). Congress, in devising a statutory framework for the review of abbreviated new animal drug applications, mandated FDA not to approve an application if the proposed labeling is not reasonably certain to be followed in practice. It did not provide any exceptions to that mandate.[2]

[2] The interpretation of the plain language of 21 U.S.C. § 360b(c)(2)(A)(ii) does not conflict with the provision permitting a generic applicant to "carve out" a portion of the reference product's label, because the latter provision does not relieve a generic application of the need to meet all other requirements for approval. *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1677 (2012) ("FDA acceptance of the carve-out label allows the generic company to place its drug on the market (*assuming the ANDA meets other requirements*)." (emphasis added).

II. Norbrook's Actions Provide Further Evidence That Norbrook's Product Will Be Used in the Field in a Single High Dose

In 2006, with no generic enrofloxacin on the market, Bayer relied on, and submitted to FDA, sworn declarations from respected veterinarians who explained, based on their years of experience in the cattle industry, that a generic version of Baytril® 100 labeled for only multi-day use in cattle nonetheless would be administered by end-users in the proscribed single-high dose. The limited experience of Norbrook's marketing of its generic Enroflox 100 product before FDA's April 19 stay of approval removed any doubt that Bayer was correct.

Notwithstanding the limitation in Norbrook's label to treatment of bovine respiratory disease with only multiple day dosing of its product, the reality in practice paints an altogether different picture. Even after a few short weeks on the market, it has become clear that end-users will view Norbrook's product as equivalent to Bayer's product, irrespective of label differences, and will administer it in a single high dose, all with Norbrook's encouragement. For example, it has come to Bayer's attention that following launch of Norbrook's Enroflox 100, one of the largest distributors of drug products for cattle (MWI/MicroBeef) requested that Norbrook's representative in Central and South Texas, Ms. MacKenzie Davis, clarify that the Enroflox 100 product was labeled only for multiple day dosing in cattle. Norbrook responded that the label so states, but that the product will be used in the field as a single high dose in cattle. Ex. 2, McNeill Decl. ¶3. Likewise, Norbrook's representative in Oklahoma, Mr. Dayton Hancock, informed at least one of Norbrook's customers after the launch that they should not worry about the label differences between Enroflox 100 and Baytril® because, among other reasons, within five to six months, the labels would be the same. Ex. 3, Brown Decl. ¶3; Ex. 4, Quade Decl. ¶¶3–4.

Actions speak louder than words. Hence Congress' mandate that FDA base its approval of new drugs on what will happen *in practice*. Theoretical or aspirational considerations, such as adherence to a labeled multiple day dosage regimen that is far less efficient and desirable than the single high dose out of respect for the law or the agency's ability to enforce essentially undetectable violations, are statutorily irrelevant. The clear superiority of single high dose administration portends such extra-label use. As Bayer's experts explained, "there is no question, that a generic multi-day enrofloxacin will be used extra-label as the protected single high dose regimen." Citizen Petition, Lewis Decl. at 2. Indeed, the United States District Court for the District of Columbia found "commonsensical [Bayer's] 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." *See* Ex. 5, *Bayer v. FDA*, Memorandum Op. at 11.

Enroflox 100 would not be reasonably certain to be used in accordance with its label (thereby precluding FDA approval) even without Norbrook's encouragement. Norbrook's conduct in the marketplace during even the first few weeks following approval—when it surely understood that its practices would be most consequential and scrutinized—confirms that such use inevitably will occur in practice.

III. Additional Information

Bayer did not include with this submission certain additional information because of restrictions established by a "Stipulated Protective Order" entered in Bayer's patent infringement

lawsuit against Norbrook in the U.S. District Court for the Eastern District of Wisconsin. *See* Ex. 6, July 10, 2009 Protective Order. Bayer sought Norbrook's consent to disclose this information to FDA, but Norbrook declined. Bayer will be able to submit this information to FDA in connection with its consideration of the Citizen Petition if FDA obtains from Norbrook permission for Bayer to do so. Please advise whether FDA has been able to obtain such permission. Otherwise, Bayer is presently unable to submit this additional information.

Respectfully submitted,

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