



December 19, 2013

Alan R. Bennett, Esq.
Ropes & Gray LLP
700 Twelfth St., N.W.
One Metro Center
Washington, D.C. 20005

Re: Citizen Petition Docket No. FDA-2006-P-0010

Dear Mr. Bennett:

This is a response to the Citizen Petition filed on June 13, 2006, by Daniel E. Troy, formerly of Sidley Austin LLP, on behalf of Bayer HealthCare, Animal Health Division (“Bayer”), Docket No. FDA-2006-P-0010 (formerly 2006-0249/CP1) (the “Petition”). You have asked that this response be addressed to you, as Bayer’s current counsel. The Petition requests that the Commissioner of Food and Drugs (the “Commissioner”) refrain from approving all future abbreviated new animal drug applications (“ANADAs”) for copies of Bayer’s Baytril® Injectable Solution. For the following reasons, the Petition is denied.

I. Factual Background

Since July 24, 1998, Bayer has held an approved new animal drug application (“NADA”) for enrofloxacin, NADA No. 141-068. The subject of that NADA is sold under the trade name Baytril® 100 Injectable Solution (“Baytril”). At the time of the Petition, Baytril was approved for use only by prescription in beef cattle for the treatment of bovine respiratory disease (“BRD”) associated with three specific bacteria: *Mannheimia haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus*. Baytril was approved for administration in beef cattle either as a multiple-dose therapy or a single-dose therapy. As acknowledged in the Petition, regulations promulgated by the Food and Drug Administration (“FDA” or “the agency”) prohibit the extralabel use of enrofloxacin in food-producing animals. See 21 Code of Federal Regulations (CFR) 522.812(d) and 530.41(a)(10).

After the Petition was filed, the agency approved two supplemental new animal drug applications that added indications for Baytril. On February 13, 2008, Baytril was approved for use only by prescription in female dairy cattle less than 20 months of age. On March 14, 2008, Baytril was approved for use only by prescription in swine as a single-dose therapy for the treatment of swine respiratory disease associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Haemophilus parasuis*, and *Streptococcus suis*.

Two relevant U.S. patents have been granted to Bayer for Baytril’s dosing regimen in cattle: (1) U.S. Patent No. 4,670,444 (the “444 patent”) covered the multiple-day dosing

therapy; and (2) U.S. Patent No. 5,756,506 (the ““506 patent”) covers the single-day dosing therapy. The ‘444 patent expired on December 9, 2006; the ‘506 patent will expire on June 27, 2015.

On February 28, 2013, FDA approved ANADA 200-495 for EnrofloxTM 100 (“Enroflox”), a generic enrofloxacin 100 mg/mL injectable solution, for the multiple-day dosing therapy in cattle and a single-dose therapy for the treatment of swine respiratory disease. Because of Bayer’s patent covering the single-dose therapy in cattle, Norbrook did not seek approval for that indication and omitted it from the proposed Enroflox labeling. *See* Norbrook comment at 2. The agency concluded that “information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that ENROFLOX 100, when used according to the label, is safe and effective.” *See* Freedom of Information Summary, ANADA 200-495, at 6.¹

On April 10, 2013, Bayer filed suit in the United States District Court for the District of Columbia, alleging that FDA violated the Federal Food, Drug, and Cosmetic Act (“FD&C Act” or “the Act”) and the Administrative Procedure Act by, among other things, approving Enroflox without issuing a final response to the Petition. *Bayer HealthCare LLC v. United States Food and Drug Administration, et al.*, C.A. No. 13-487 (RMC) (D.D.C.). On April 19, 2013, the Commissioner decided to reconsider the approval of ANADA 200-495 for Enroflox for use in cattle, including the approval of the labeling that refers to the use of Enroflox in cattle. To permit this reconsideration, FDA stayed the approval of ANADA 200-495 for use of Enroflox in cattle, including the approval of labeling that refers to the use of Enroflox in cattle, until FDA completes its consideration of the issues raised in the Petition and the application. On April 24, 2013, the Court remanded the case to FDA for reconsideration of its approval of ANADA 200-495 for use of Enroflox in cattle and the approval of labeling that refers to the use of Enroflox in cattle.

Bayer’s principal argument is that a statutory provision that requires FDA to approve a generic animal drug application unless it finds that “the conditions of use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice” protects Bayer from generic competition until its patent on a single-dose regimen in cattle expires. Bayer reasons that even if generic drugs are approved only for those indications that are not protected by patent, carving out the single dose regimen, the drugs nevertheless will be used for the protected indication. As discussed below, (1) when viewed in the context of the entire statute and legislative history, it is clear that the quoted language was intended to serve a purpose other than, as Bayer suggests, protecting an innovator drug maker’s monopoly, and (2) even if Bayer’s interpretation were accepted, FDA lacks a scientific basis to support a finding that the conditions of use recommended in the proposed labeling are not reasonably certain to be followed in practice. In responding to the Petition, FDA considered Bayer’s submissions as well as other comments submitted to the docket.

¹ Available at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM351212.pdf>.

II. Legal Background

A. Section 512 of the FD&C Act

Section 512 (21 U.S.C. § 360b) was added to the FD&C Act through the Animal Drug Amendments of 1968. P. L. 90-399 (July 13, 1968). Prior to the Animal Drug Amendments of 1968, animal drug manufacturers were required to obtain approval to market drugs for food-producing animals under section 505 of the FD&C Act (21 U.S.C. § 355), to establish safety and effectiveness in the target animal, and under section 409 of the FD&C Act (21 U.S.C. § 348), to establish human food safety. Section 512 consolidates provisions for the safety and effectiveness of new animal drugs, creating a single streamlined approval process.

B. Generic new animal drugs

In 1988, Congress passed the Generic Animal Drug and Patent Term Restoration Act (“GADPTRA”), P.L. 100-670, “to create in the animal drug industry the same conditions for generic drugs and patent term restoration as Congress did in the human drug industry in 1984” H. Rep. No. 100-972(II), at 14 (1988), *reprinted in* 1988 U.S.C.C.A.N. 5659, 5668. Congress recognized that requiring generic applicants to duplicate the innovator’s safety and effectiveness studies is “in effect, a secondary patent--that protects the brand name animal drug indefinitely from generic competition.” *Id.* at 15. Therefore, as with generic human drugs, a generic animal drug applicant could reference FDA’s safety and effectiveness determination for the corresponding innovator drug:

An abbreviated new animal drug application does not contain the data on safety and efficacy that were required in the full new animal drug application to market the original or brand name animal drug. This expedited procedure is predicated on the view that the safety and effectiveness of the animal drug have already been established. *Id.*

An overarching goal of the new abbreviated pathway was to increase drug availability by encouraging competition and lowering prices. *Id.* at 16. Congress created balance in the law by extending the length of patents, in order to restore incentives for innovation and research for new animal drug products. *Id.*

In general, a generic new animal drug must be the same as a previously approved new animal drug (the “reference listed new animal drug” or “RLNAD”). Section 512(n)(1) of the FD&C Act (21 U.S.C. § 360b(n)(1)) sets forth the required contents of an ANADA, including information showing that: the conditions of use or similar limitations have been previously approved for the RLNAD (§ 512(n)(1)(A)(i) (21 U.S.C. § 360b(n)(1)(A)(i))); the withdrawal period at which residues of the generic drug will be consistent with the tolerances established for the RLNAD (§ 512(n)(1)(A)(ii) (21 U.S.C. § 360b(n)(1)(A)(ii))); the active ingredients are the same as the RLNAD (§ 512(n)(1)(B)(i) (21 U.S.C. § 360b(n)(1)(B)(i))); the route of administration, dosage form, and the strength are the same as the RLD (§ 512(n)(1)(D) (21 U.S.C. § 360b(n)(1)(D))); the generic drug is bioequivalent to the RLNAD (§ 512(n)(1)(E) (21

U.S.C. § 360b(n)(1)(E)); and the proposed labeling is the same as the RLNAD (§ 512(n)(1)(F) (21 U.S.C. § 360b(n)(1)(F)).

However, there are exceptions to some of these sameness requirements. For example, GADPTRA permits generic applicants to propose a different withdrawal period from the RLNAD for a generic new animal drug that is bioequivalent to the RLNAD so long as the residues of the generic drug are consistent with the tolerances established for the RLNAD. *See* FD&C Act § 512(n)(1)(A)(i) and § 512(c)(2)(B) (21 U.S.C. § 360b(c)(2)(B)). In addition, a generic animal drug may have different labeling than the RLNAD in certain circumstances, including when labeling differences are “required because . . . the drug and the approved new animal drug are produced or distributed by different manufacturers.” FD&C Act § 512(c)(2)(A)(vii) (21 U.S.C. § 360b(c)(2)(A)(vii)). One important labeling difference that falls into this category is a “carve out.” The legislative history of GADPTRA makes clear that Congress intended to allow generic applicants to obtain approval for fewer than all of the RLNAD’s indications where the remaining indications are protected by patent, and to “carve” the protected indications “out” of their labeling:

The applicant need not seek approval for all the conditions of use for which the brand name animal drug has been approved. For example, if the brand name animal drug has been approved for use in multiple species, one use of which is protected by patent, the applicant may seek approval for only the non-patented conditions. The labeling of such a generic animal drug for only the non-patented conditions would be in compliance with the labeling requirement of the section. H. Rep. No. 100-972(II), at 18.²

Consistent with the Act and the legislative history, if a condition of use for which an NADA is approved remains protected by patent, an ANADA may omit that condition of use from its proposed labeling.

Also important here is that GADPTRA prohibits FDA from requiring generic sponsors to submit information beyond what is specified in section 512(n)(1). FD&C Act § 512(n)(1).

C. Sections 512(d) and 512(c)(2): Whether proposed conditions of use are reasonably certain to be followed in practice

Section 512(d)(1) of the FD&C Act (21 U.S.C. § 360b(d)(1)) sets forth the circumstances under which FDA shall refuse to approve an NADA. One such circumstance is when the investigations supporting approval:

do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed,

² Congress thus intended that this provision concerning the labeling of generic animal drugs be interpreted in the same way that the parallel provision relating to generic human drugs is interpreted. *See* 21 CFR 314.94(a)(8)(iv) (differences required because drugs are produced or distributed by different manufacturers include, among others, “omission of an indication or other aspect of labeling protected by patent or accorded exclusivity”).

recommended, or suggested in the proposed labeling thereof. FD&C Act § 512(d)(1)(A) (21 U.S.C. § 360b(d)(1)(A)).

In determining whether an animal drug is “safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof,” FDA considers “whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice.” FD&C Act § 512(d)(2)(D) (21 U.S.C. § 360b(d)(2)(D)). This language derives from the food additive safety provisions of section 409 of the FD&C Act. *See, e.g.*, H. Rep. No. 90-875, at 5 (1967).

Similarly, under section 512(c)(2)(A) of the FD&C Act (21 U.S.C. § 360b(c)(2)(A)), FDA must approve an ANADA unless the agency finds, among other things, that:

(ii) the conditions of use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice or, except as provided in subparagraph (B),³ information submitted with the application is insufficient to show that each of the proposed conditions of use or similar limitations (whether in the labeling or published pursuant to subsection (i))⁴ have been previously approved for the approved new animal drug referred to in the application. (emphasis added)

FDA’s interpretation of this provision is explained in greater detail below.

D. Animal Medicinal Drug Use Clarification Act of 1994

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) amended the FD&C Act to allow veterinarians to prescribe extralabel uses of certain approved animal drugs and approved human drugs for animals under certain conditions. *See* FD&C Act §§ 512(a)(4) and 512(a)(5) (21 U.S.C. §§ 360b(a)(4) and (a)(5)). Extralabel use refers to the actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. 21 CFR 530.3(a). Under AMDUCA, extralabel use must be by or on the order of a veterinarian within the context of a veterinarian-client-patient relationship, must not result in violative residues in food-producing animals, and must be in conformance with the implementing regulations published at 21 CFR Part 530. *See* FD&C Act § 512(a)(4)(A) & (B).

³ Section 512(c)(2)(B) of the FD&C Act allows FDA to establish a different withdrawal period for a generic new animal drug than its reference listed new animal drug, on the basis of information submitted, if the generic drug is bioequivalent to the reference listed new animal drug and the residues of the generic drug are consistent with the tolerances established for the reference listed new animal drug at that different withdrawal period.

⁴ Section 512(i) of the FD&C Act (21 U.S.C. § 360b(i)) requires FDA to publish a notice in the Federal Register once a new animal drug application is approved with the name and address of the applicant, as well as “the conditions and indications of use of the new animal drug covered by such application, including any tolerance and withdrawal period or other use restrictions,” among other things.

These regulations include a list of drugs that FDA has specifically prohibited from extralabel use. Fluoroquinolones, a class of antibiotic drugs that includes enrofloxacin, are on this list. 21 CFR 530.41(a)(10).

III. Arguments Presented in the Petition and Supplementary Submissions

In the Petition, Bayer asks that the Commissioner deny all future ANADAs for generic versions of Baytril. Bayer claims that “[i]t is reasonable to conclude that any generic [enrofloxacin] approved for the Multiple-Day dosing regimen,” which lost patent protection on December 9, 2006, “would likely be used as a Single-Dose” product, pursuant to the dosing regimen that remains protected under the ‘506 patent. Bayer contends that approval of any enrofloxacin ANADA for the multiple-day dosing regimen is prohibited by GADPTRA, because, according to Bayer, it is not reasonably certain that the conditions of use prescribed in the generic’s proposed labeling will be followed in practice.

To support its contention regarding the likelihood of extralabel use, Bayer submitted the results of a survey conducted by Doane Marketing Research (“Doane”) of 250 range and feedlot veterinarians administering and/or prescribing Baytril. Bayer claims that the research shows that 72-76% of the cattle treated with Baytril for BRD received a single dose, whereas 24-28% received the multiple-day dose. Bayer also attached to the Petition three declarations from practicing veterinarians in support of Bayer’s contention that a generic enrofloxacin product approved only for the multiple-day dosing regimen would be used off-label for the single-dose regimen.

Bayer also argues that the Commissioner should deny all future ANADAs that reference Baytril because “there is little guarantee that any other company” would implement a post-approval monitoring program and controlled distribution system like Bayer’s.

On May 6, 2013, Bayer submitted a supplement to the Petition (“Bayer Supplement”). There, Bayer contends that “[t]he statute is unambiguous and permits no other interpretation” than to prohibit FDA from approving a generic application if the generic drug product is not reasonably certain to be used according to its labeling in practice. Bayer recognizes that the language at issue also appears in section 512(d) of the FD&C Act, which sets forth bases for rejecting a new animal drug application. Bayer contends that because that language in section 512(d) is explicitly part of the agency’s consideration of a new animal drug’s safety, and there is no explicit reference to safety in section 512(c)(2)(A)(ii) (21 U.S.C. § 360b(c)(2)(A)(ii)), the prohibition of ANADA approval based on the likelihood of off-label use set forth in 512(c)(2)(A)(ii) is unconditional. In addition, because section 512(c)(2)(A)(ii) relates to whether the proposed labeling will be followed “in practice,” Bayer argues that “theoretical or aspirational considerations, such as adherence to a labeled multiple day dose 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.” Finally, Bayer claims that in the few weeks that Enroflox was on the market, Norbrook promoted the product for the single dose in cattle. These claims were contested by Norbrook in its submission to the docket dated May 16, 2013.

On July 8, 2013, Bayer submitted a letter directing FDA's attention to its July 8, 2013 Reply in Support of its Rule 60(a) Motion in *Bayer HealthCare LLC v. United States Food and Drug Administration, et al.*, C.A. No. 13-487 (RMC) (D.D.C.) ("Bayer's Motion"). Bayer's Motion [REDACTED]

[REDACTED] On July 15, 2013, the Court issued an order granting Bayer's Motion, permitting Bayer to file a reply brief in support of its motion for preliminary injunction in the *Bayer HealthCare LLC v. United States Food and Drug Administration, et al.* litigation.

On July 24, 2013, Bayer submitted a letter directing FDA's attention to its July 19, 2013 Reply in Support of its Motion for Preliminary Injunction and 390 appended exhibits in the *Bayer HealthCare LLC v. United States Food and Drug Administration, et al.* litigation ("Bayer Reply"). Bayer's Reply asserts [REDACTED]

[REDACTED] Bayer appends exhibits from [REDACTED] experts submitted during its patent litigation with Norbrook [REDACTED]

[REDACTED] Bayer also appends additional exhibits that, [REDACTED]

[REDACTED] Bayer also appends exhibits in which its experts opine [REDACTED]

[REDACTED] Bayer's claims were contested by Norbrook in its submission to the docket dated August 16, 2013.

On September 12, 2013, Bayer submitted an additional supplement to the Petition ("Bayer Supplement 2") in response to an August 16, 2013 submission to the docket by Norbrook. Bayer reiterates its core factual allegation, that Enroflox, if approved, would be used off-label in cattle in a single dose, even if it were only labeled for multiple dose treatment in cattle. Bayer also argues that the FD&C Act does not allow FDA to presume that end users of Enroflox will in practice follow its label. Responding to an argument by Norbrook that section 512(c)(2)(A)(ii) applies where there are differences in the proposed conditions of use between an ANADA and its RLNAD, Bayer argues that section 512(c)(2)(A)(ii) generally "applies irrespective of whether or not the conditions of use on the generic label differ from those on the reference listed product's label," based on the absence of explicit statutory language limiting the applicability of 512(c)(2)(A)(ii) in the way Norbrook suggests. See Bayer Supplement 2 at 9. Bayer also contends that there is no tension between its proffered reading of section 512(c)(2)(A)(ii) and AMDUCA, and that even if there were any tension between the two provisions, section 512(c)(2)(A)(ii) would control under the canon that specific terms in a statute govern more general ones.

IV. Discussion

A. In the context of the entire statute and legislative history, it is clear that the language at issue was intended to serve a purpose other than, as Bayer suggests, protecting an innovator drug maker's monopoly.

As discussed above, section 512(c)(2)(A) of the FD&C Act requires FDA to approve an ANADA unless it finds, among other things, that:

(ii) the conditions of use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice or, except as provided in subparagraph (B), information submitted with the application is insufficient to show that each of the proposed conditions of use or similar limitations (whether in the labeling or published pursuant to subsection (i)) have been previously approved for the approved new animal drug referred to in the application. (emphasis added)

Bayer asserts that the underlined language imposes an “unconditional prohibition” of ANADA approval “based on the likelihood of off-label use alone.” Bayer Supplement at 2. However, as set forth more fully below, section 512(c)(2)(A)(ii)’s first clause cannot reasonably be interpreted to require FDA to refuse to approve an ANADA solely because an extralabel use may occur. Consistent with the text, purpose, and structure of GADPTRA and related FD&C Act provisions, FDA interprets section 512(c)(2)(A)(ii)’s first clause to apply where an ANADA proposes a different condition of use, namely a different withdrawal period, from the RLNAD. The provision authorizes disapproval of the ANADA where FDA finds that the different proposed withdrawal period is not reasonably certain to be followed in practice, creating a potential human food safety concern.

1. Bayer’s interpretation of section 512(c)(2)(A)(ii) is untenable.

Bayer asserts that section 512(c)(2)(A)(ii) is “unambiguous and permits no other interpretation” than to prohibit approval of an ANADA where there is a high likelihood of extralabel use. Essentially, Bayer interprets section 512(c)(2)(A)(ii) to provide additional exclusivity to a brand name drug where a generic drug is likely to be used in an extralabel manner. FDA finds Bayer’s interpretation to be unconvincing because it is contrary to the text, purpose, legislative history, and structure of GADPTRA and conflicts with the framework for extralabel use under AMDUCA.

(a) Bayer’s interpretation would undermine GADPTRA’s carve-out provision.

GADPTRA permits a generic applicant to seek approval for a subset of the RLNAD’s approved conditions of use where the remaining conditions of use are protected by patent. *See* FD&C Act § 512(n)(1)(F); H. Rep. No. 100-972(II), at 18 (“The applicant need not seek approval for all the conditions of use for which the brand name animal drug has been approved.”). The House Report provides the following example of how GADPTRA’s carve-out

provision works in practice: “[I]f the brand name animal drug has been approved for use in multiple species, one use of which is protected by patent, the [generic] applicant may seek approval for only the non-patented conditions.” *Id.* Without the possibility of such a carve-out, generic new animal drugs effectively would be barred from the market until every patent on every condition of use on the RLNAD label expires. Brand name animal drugs would have an incentive to add additional patented claims at a trickle, over the greatest period of time possible, maintaining complete market exclusivity the entire time. As a result, competition would be minimized and innovation would be slowed, the opposite of GADPTRA’s intent.

Bayer does not dispute that GADPTRA allows for ANADAs to carve-out on-patent uses. *See, e.g.*, Bayer Reply at 7.⁵ However, even Bayer strains to explain how its interpretation does not eviscerate the carve-out provision entirely. Bayer asserts that its interpretation does not create tension with the carve-out provision because section 512(c)(2)(A)(ii)’s first clause would not bar ANADA approval in “more typical circumstances” “where the carved-out use is different rather than superior to the labeled use or does not constitute the large majority of the branded product’s use[.]” Bayer Reply at 7. However, it is unclear how Bayer generated these limitations, aside from the fact that they seem conveniently tailored to the situation at hand. In fact, one might think that extralabel use is less likely here than in “more typical circumstances,” given that extralabel use of enrofloxacin is expressly prohibited under FDA regulations. Bayer makes a variant of an argument that FDA has encountered, and successfully rebuffed, in the human generics context; Bayer “in essence wants foreseeable off-label use to bar the approval of generic drugs, even for unprotected indications.” *Sigma-Tau Pharmaceuticals v. Schwetz*, 288 F.3d 141, 147 (4th Cir. 2002). Bayer’s interpretation would reduce the ability of generic applicants to carve out protected uses and lead to lengthy, unintended monopolies for innovator animal drugs, limiting generic drug availability.

(b) GADPTRA’s legislative history and structure demonstrate that section 512(c)(2)(A)(ii) is not an additional exclusivity provision.

In addition to the carve-out provision, it is clear that Congress did not intend section 512(c)(2)(A)(ii) to be an additional exclusivity provision for brand-name animal drugs from the relationship between GADPTRA and the Hatch-Waxman Amendments, the legislative history of section 512(c)(2)(A)(ii), and the structure of GADPTRA. Bayer’s reading of section 512(c)(2)(A)(ii) would undermine Congress’s express purpose in enacting GADPTRA, “to create in the animal drug industry the same conditions for generic drugs and patent term restoration as Congress did in the human drug industry in 1984” through the Hatch-Waxman Amendments. H. Rep. No. 100-972(II), at 15. Under Bayer’s interpretation, section 512(c)(2)(A)(ii) would confer upon brand-name animal drugs a form of marketing exclusivity that is not available to brand-name human drugs. Bayer provides no explanation for why Congress, in enacting legislation based on the Hatch-Waxman Amendments, would provide brand-name animal drug sponsors with a marketing exclusivity that was not part of the Hatch-

⁵ Indeed, by virtue of its acquisition of Teva Animal Health, Bayer owns an ANADA for Ivermectin Injectable (ANADA 200-228) that came to market with less than the full indications of the brand-name animal drug, the very practice that Bayer now decries as contrary to the statute. If Bayer’s interpretation of section 512(c)(2)(A)(ii) were correct, this approved ANADA would have been subject to disapproval if there were a reasonable likelihood that the drug would have been used extralabelly for the carved-out use.

Waxman Amendments, and no such cogent reason exists. For human drugs, the Hatch-Waxman Amendments struck a careful balance between providing additional incentives for innovators and increasing generic competition to lower costs and improve drug availability. GADPTRA was explicitly intended to do the same for animal drugs. Bayer's interpretation threatens to disrupt the balance that Congress intended by applying section 512(c)(2)(A)(ii) to extend exclusivity for uses that are not protected by patent and are not otherwise entitled to exclusivity under the FD&C Act.

Indeed, interpreting section 512(c)(2)(A)(ii) as a marketing exclusivity provision is not supported by the legislative history of that section. The "conditions of use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice" language was not part of the initial GADPTRA legislation introduced in Congress. *See, e.g.*, S. 2407, 99th Cong. § 103(c)(4)(B) (1986) (as introduced by Sen. Hatch); H.R. 5069, 99th Cong. § 101(c)(2)(A)(ii) (1986) (as introduced by Rep. Waxman). Rather, this provision was added to GADPTRA after the legislation was reported to the House by the House Committee on Energy and Commerce in September 1988. *See* H.R. 4982, 100th Cong. § 512(c)(2)(A)(ii) (as reported by the House Committee on Energy and Commerce); H.R. 4982, 100th Cong. § 512(c)(2)(A)(ii) (as reported by the House Committee on the Judiciary) (containing the entirety of the language that would become section 512(c)(2)(A)(ii)). The legislative history indicates that this "conditions of use" amendment was "endorse[d] without qualification" by the Generic Pharmaceutical Industry Association--an industry association that would have had an economic interest in opposing the amendment, if it truly had been intended to give pioneer products additional, even lifetime, market exclusivity. *See* Generic Animal Drug and Patent Term Restoration Act: Hearing on H.R. 4982 Before the Subcomm. on Courts, Civil Liberties and the Admin. of Justice of the H. Comm. on the Judiciary, 100th Cong. 124 n.2 (1988) (statement of Jess Stribling, counsel, Generic Pharmaceutical Industry Association).⁶

The structure of GADPTRA provides more evidence that Congress did not intend section 512(c)(2)(A)(ii) to provide another mechanism for extending an innovator's monopoly. Section 512(c)(2)(A)(ii) is located within section 512(c)(2)(A), which specifies eleven grounds for denying approval of a generic animal drug based on the safety or effectiveness of the drug or the sameness of the drug to the RLNAD. By contrast, none of the provisions of section 512(c)(2)(A) relate to market exclusivity or patent extension. GADPTRA's market exclusivity provisions are found in section 512(c)(2)(F) (21 U.S.C. § 360b(c)(2)(F)), while GADPTRA's patent term restoration provisions appear in the patent statutes rather than in the FD&C Act. *See* 35 U.S.C. § 156; GADPTRA, Pub. L. No. 100-670, tit. II. Bayer's contention that Congress tucked a

⁶ The relevant testimony from Generic Pharmaceutical Industry Association is as follows: "There are two amendments in Title I pertaining to grounds for denial of an abbreviated application for a generic new animal drug that GPIA endorses without qualification. One of these provides that FDA may deny approval of an abbreviated application if, based on a fair evaluation of all material facts, the proposed labeling of the generic is false or misleading in any particular. The other provides that FDA may deny approval unless the conditions for use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice. It is our understanding that the Food and Drug Administration concurs with these amendments."

market exclusivity provision in with eleven grounds for denying approval of a ANADA is belied by the structure of GADPTRA.

(c) Bayer's interpretation would create a barrier to approval of generic animal drugs that does not exist for brand-name animal drugs.

In addition, interpreting section 512(c)(2)(A)(ii)'s first clause as an "unconditional prohibition" on ANADA approval based on the likelihood of extralabel use would frustrate the purpose of GADPTRA by creating a barrier to approval of generic animal drugs that does not exist for brand-name animal drugs. *See H. Rep. No. 100-972(II)* at 15 (stating that GADPTRA's abbreviated generic application procedure is intended to remove "barrier[s] to market entry . . . that protect[] the brand name animal drug indefinitely from generic competition."). Under Bayer's interpretation, the same likelihood of legal, extralabel use could mandate different approval decisions for an NADA and an ANADA, even where the generic product is an exact copy of the RLNAD. Under Bayer's view, a reasonable certainty of extralabel use would not bar approval of an NADA so long as the extralabel use does not affect safety (under section 512(d)(2)), while the same likelihood of the same extralabel use would bar approval of an ANADA. It is incongruous to suppose that a statute intended to remove "requirements . . . that protect[] the brand name animal drug indefinitely from generic competition," *H. Rep. No. 100-972(II)* at 15, would create a new requirement that would protect brand name animal drugs indefinitely from generic competition when that brand name drug is used in an extralabel manner.

(d) Bayer's interpretation would require FDA to conduct a duplicative review of conditions of use that it previously approved for the RLNAD.

Bayer's interpretation of section 512(c)(2)(A)(ii)'s first clause would also require FDA to review the same conditions of use for the generic that it previously approved for the RLNAD. Section 512(d)(2)(D) requires FDA to consider "whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice" in determining whether a new animal drug is safe. Under Bayer's interpretation, section 512(c)(2)(A)(ii) would require FDA to review all of the generic's conditions of use, including to re-review conditions of use that are the same between the generic and the RLNAD.

Requiring FDA to perform a duplicative review for a generic drug application is contrary to an explicit purpose of GADPTRA, which was to create an "expedited procedure" for generic approvals "predicated on the view that the safety and effectiveness of the animal drug have already been established." *H. Rep. No. 100-972(II)*, at 15. Consistent with this framework, GADPTRA requires sponsors to submit information showing that various components of their applications, including a generic's conditions of use -- with the exception of allowable differences in withdrawal periods -- have been previously approved. *See FD&C Act § 512(n)(1)(A) (21 U.S.C. § 360b(n)(1)(A)).* Generic sponsors, in general, do not submit safety and effectiveness data; they demonstrate bioequivalence to the RLNAD. The generic drug review process is focused on determining that a generic drug is the same as the RLNAD, and such a determination obviates the need for duplicative submissions or review. As interpreted by Bayer, section 512(c)(2)(A)(ii)'s first clause would be inexplicably the only provision in

GADPTRA to require FDA to conduct a duplicative review of elements of the RLNAD's NADA review. There is no indication that Congress intended section 512(c)(2)(A)(ii) to be interpreted this way.

(e) Because AMDUCA authorizes certain extralabel use, the likelihood of extralabel use cannot trigger disapproval of an ANADA.

GADPTRA cannot be interpreted to impose an “unconditional prohibition” of ANADA approval “based on the likelihood of off-label use alone,” as Bayer urges, without creating a conflict between GADPTRA and AMDUCA. Congress expressly authorized certain extralabel use in AMDUCA. The conditions on extralabel use that AMDUCA established do not focus on the likelihood of a particular use. Instead, they relate to ensuring veterinarian oversight and protecting human food safety. *See FD&C Act § 512(a)(4)(A).* Under this framework, the extralabel use of fluoroquinolones, such as enrofloxacin, is explicitly prohibited by FDA regulations. *See 21 CFR 522.812(d) & 530.41(a)(10).* As applied to other animal drug products, however, Bayer’s interpretation of section 512(c)(2)(A)(ii) would require FDA to disapprove a generic drug application where extralabel use authorized by AMDUCA is likely. In other words, Bayer’s interpretation essentially would remove generic drugs from the extralabel use scheme established through AMDUCA.⁷

Nothing in the AMDUCA legislative history suggests that Congress understood its provisions authorizing extralabel use would in practice apply to pioneer drugs and not to generic drugs. The legislative history of AMDUCA simply indicates that Congress intended to allow the extralabel use of drugs by veterinarians under certain circumstances and to prohibit extralabel use resulting in residues that could pose a human food safety concern. *See 140 Cong. Rec. 28661 (1994)* (statement of Rep. Henry Waxman) (“I believe that this bill strikes the appropriate balance between the need of veterinarians and the need to protect the food supply. It will permit veterinarians to use drugs for unapproved uses, while giving the FDA the authority to regulate those uses and to impose requirements to protect the public health where appropriate.”). More specifically, there is no suggestion that Congress, in drafting AMDUCA, believed that section 512(c)(2)(A)(ii) barred ANADA approval based on the likelihood of off-label use and that AMDUCA would therefore apply essentially to brand-name animal drugs, not generics.

⁷ Bayer’s interpretation of section 512(c)(2)(A)(ii) creates additional tension with AMDUCA because of the evidentiary findings it would require FDA to make in determining whether a generic drug is reasonably likely to be used extralabelly. In the case of fluoroquinolones, for which extralabel use is illegal under the AMDUCA regulations, Bayer asks FDA to find that [REDACTED]

[REDACTED] It is unclear how an administrative agency is to analyze evidence that is premised on the belief that the agency will not enforce the laws it is charged to enforce. This is particularly true where FDA could take multiple actions to change the public’s perception including, for example, publicizing the enforcement of certain violations. Basing an approval decision on a factor that is mutable and subject to FDA’s influence seems problematic. Because the extra-label use of other animal drugs is illegal under AMDUCA, under Bayer’s reading of section 512(c)(2)(A)(ii), FDA would perform this analysis for other ANADAs as well.

Bayer contends that any conflict between its interpretation of section 512(c)(2)(A)(ii) and AMDUCA should be resolved in favor of section 512(c)(2)(A)(ii) under the canon that specific terms in a statute govern more general ones. Bayer Supplement 2 at 10. But this canon is inapplicable here, where any conflict between the provisions can be harmonized. *See, e.g.*, *N.A.A.C.P., Detroit Branch v. Detroit Police Officers Ass'n*, 900 F.2d 903, 912 (6th Cir. 1990); Norman J. Singer, *Sutherland on Statutory Construction* § 51.05 (7th ed. 2012) ("Where one statute deals with a subject in general terms, and another deals with a part of the same subject in a more detailed way, the two should be harmonized if possible;"). As noted, *infra* p. 18, FDA's interpretation of section 512(c)(2)(A)(ii) does not create any conflict between the first prong of section 512(c)(2)(A)(ii) and AMDUCA. By creating a conflict between section 512(c)(2)(A)(ii) and AMDUCA, Bayer's interpretation of section 512(c)(2)(A)(ii) violates the principle that a statute is to be interpreted "as a symmetrical and coherent regulatory scheme and fit, if possible, all parts into a harmonious whole." *Brown & Williamson Tobacco Corp.*, 539 U.S. at 133.

2. The text, structure, and legislative history of GADPTRA demonstrate that section 512(c)(2)(A)(ii)'s first clause is properly interpreted to apply where FDA finds that an ANADA's proposed different withdrawal period is not reasonably certain to be followed in practice.

Section 512(c)(2)(A)(ii)'s first clause must be construed within the context of GADPTRA, the Hatch-Waxman Amendments on which GADPTRA is modeled, and the FD&C Act as a whole. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) ("the words of a statute must be read in their context and with a view to their place in the overall statutory scheme") (internal citation omitted). This principle gives rise to certain considerations that govern how section 512(c)(2)(A)(ii) is interpreted. First, section 512(c)(2)(A)(ii)'s first clause should be read in light of the entirety of section 512(c)(2)(A)(ii) and related provisions, including sections 512(c)(2)(B) and 512(n)(1)(A)(i). Second, the interpretation of section 512(c)(2)(A)(ii) should not give rise to a higher standard for approving a generic drug than a brand name drug. Third, it should not require a generic sponsor to duplicate studies or FDA to duplicate a review that it already conducted as to the RLNAD. Fourth, because the provision has no counterpart in the human generic drug provisions of the FD&C Act, section 512(c)(2)(A)(ii)'s interpretation must be unique to animal drugs. Fifth, the provision should be read in light of how Congress used the same or similar language elsewhere in the FD&C Act. Based on these considerations, FDA interprets the first clause of section 512(c)(2)(A)(ii) to apply where an ANADA proposes a different withdrawal period from the RLNAD, and FDA finds that the proposed withdrawal period is not reasonably certain to be followed in practice.

First, section 512(c)(2)(A)(ii)'s first clause should be read in light of the entirety of section 512(c)(2)(A)(ii) and related provisions, including section 512(c)(2)(B) and section 512(n)(1)(A)(i). As set forth above, in determining whether a brand name new animal drug is "safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof," FDA considers "whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice." FD&C Act § 512(d)(2)(D). Section 512(n)(1)(A)(i) requires generic applicants to submit information to FDA showing that the proposed conditions of use have been previously approved for the RLNAD,

with one exception. Correspondingly, the second clause of section 512(c)(2)(A)(ii) authorizes FDA to disapprove ANADAs where the generic applicant fails to show that each of its proposed conditions of use have been previously approved for the RLNAD, with the same exception. GADPTRA permits generic applicants to propose a different withdrawal period from the RLNAD for a generic drug that is bioequivalent to the RLNAD so long as the residues of the generic drug are consistent with the tolerances established for the RLNAD, *see FD&C Act §§ 512(n)(1)(A)(i), 512(c)(2)(A)(ii), and 512(c)(2)(B)*.

FDA already considered under section 512(d)(2)(D), during its review of the RLNAD, whether those conditions of use that are the same between the generic and the RLNAD are reasonably certain to be followed in practice. However, where the generic new animal drug is proposing a new condition of use – a new withdrawal period – FDA must consider for the first time whether the different withdrawal period would be “reasonably certain to be followed in practice” in order to ensure that the generic drug is as safe as the RLNAD. Section 512(c)(2)(A)(ii) provides FDA that authority. Depending on the proposed withdrawal period in question, FDA could have concerns about whether the withdrawal period was compatible with industry production practices, for example. Not following a withdrawal period can create a human food safety hazard. For example, most drugs used in broiler chickens have short withdrawal periods (from 0 to 5 days); broiler chickens are typically slaughtered at 5 to 6 weeks of age. If a generic copy of a brand-name drug used in broiler chickens required a 60 day withdrawal period to reach safe residue concentrations, an end user would need to delay slaughter until well beyond the standard industry practice in order to use the drug in accordance with its label. The withdrawal period is not reasonably certain to be followed in practice, and FDA’s approval of the drug could result in unsafe drug residues in the edible tissue of broiler chickens. Without the first clause of section 512(c)(2)(A)(ii), FDA would have no explicit authority to disapprove an ANADA containing a proposed different withdrawal period that is not reasonably certain to be followed in practice. Because sections 512(n)(1)(A)(i) and 512(c)(2)(B) authorize generic applicants to propose different withdrawal periods from the RLNAD, and such different withdrawal periods are expressly exempt from the second clause of section 512(c)(2)(A)(ii), the first clause of section 512(c)(2)(A)(ii) permits FDA to consider whether a generic’s different withdrawal period is reasonably certain to be followed in practice. Without the first clause of section 512(c)(2)(A)(ii), the generic new animal drug approval process would have a human food safety gap.⁸ Section 512(c)(2)(A)(ii) helps ensure that generic new animal

⁸ FDA’s interpretation of section 512(c)(2)(A)(ii)’s first clause is consistent with the legislative history of that clause. The initial Senate version of GADPTRA introduced in 1986 contained only the second clause of what would become section 512(c)(2)(A)(ii), and not the first clause or the section 512(c)(2)(B) proviso. *See S. 2407, 99th Cong. § 103(c)(4)(B) (1986)* (as introduced by Sen. Hatch). The initial House version of GADPTRA contained the second clause and section 512(c)(2)(B) proviso but also did not contain the language that would become section 512(c)(2)(A)(ii)’s first clause. *See H.R. 5069, 99th Cong. § 101(c)(2)(A)(ii) (1986)* (as introduced by Rep. Waxman). The first clause of what would become section 512(c)(2)(A)(ii) was not added to GADPTRA until after the legislation was reported to the House by the House Committee on Energy and Commerce in September 1988. *See H.R. 4982, 100th Cong. § 512(c)(2)(A)(ii)* (as reported by the House Committee on Energy and Commerce); *H.R. 4982, 100th Cong. § 512(c)(2)(A)(ii)* (as reported by the House Committee on the Judiciary) (containing the entirety of the language that would become section 512(c)(2)(A)(ii)). This legislative history suggests that Congress added section 512(c)(2)(A)(ii)’s first clause to address issues that cropped up during the GADPTRA drafting process, such as ensuring that the different proposed withdrawal period authorized

drugs are just as safe as their RLNADs, even when they require withdrawal periods that have not been previously approved.

Bayer argues that the first clause of section 512(c)(2)(A)(ii) must be interpreted to apply irrespective of whether the conditions of use differ between the generic and the RLNAD, because of the absence of such limiting statutory language. In making this argument, Bayer interprets the first clause of section 512(c)(2)(A)(ii) in a vacuum and creates conflict with other statutory provisions as shown above. FDA's interpretation makes sense of section 512(c)(2)(A)(ii) in context and allows the statute to be read as a harmonious whole while avoiding the consequence of Bayer's interpretation that entry of animal generic drugs to the market can be indefinitely forestalled by serially adding new indications.

Second, FDA's interpretation of section 512(c)(2)(A)(ii)'s first clause is consistent with the second consideration set forth above: the provision should not be interpreted to require a generic drug sponsor to repeat studies conducted by the RLNAD sponsor or require FDA to duplicate a review that it already conducted as to the RLNAD. A purpose of GADPTRA was to create an expedited procedure for the approval of generic animal drugs that avoids "repetition of the costly and time-consuming studies that are typically required to establish safety and effectiveness," because it constitutes a barrier to entry for "generic duplicates" and because "a requirement for duplicative studies is scientifically unnecessary and ethically questionable." H. Rep. No. 100-972(II), at 15. A duplicative review by FDA is similarly costly for the taxpayer, time-consuming for the agency and the applicant, and scientifically unnecessary; the applicant need only demonstrate that its drug is, in fact, a "generic duplicate." Under FDA's interpretation of section 512(c)(2)(A)(ii), the first clause of section 512(c)(2)(A)(ii) applies where a proposed condition of use is different than the conditions of use previously approved for the RLNAD; the second clause of section 512(c)(2)(A)(ii) holds the generic drug applicant accountable for showing that all conditions of use, except the withdrawal period, have been previously approved. Therefore, under FDA's interpretation of section 512(c)(2)(A)(ii), FDA does not conduct duplicative reviews or require duplicative information from the generic sponsor. Instead, section 512(c)(2)(A)(ii) provides the agency the authority to consider for the first time whether the ANADA's proposed different withdrawal period is reasonably certain to be followed in practice.

Third, FDA's interpretation of section 512(c)(2)(A)(ii) does not require a higher standard for approving an animal generic drug than for approving a brand name animal drug. GADPTRA established an abbreviated pathway for generic drugs that duplicate brand name drugs, "predicated on the view that the safety and effectiveness of the animal drug have already been established." H. Rep. 100-972(II), at 15. Interpreting the statute to require a higher approval standard for generic drugs than brand name drugs could bar generic market entry where the generic and pioneer are duplicates. *See* H. Rep. No. 100-972(II), at 15 (noting that a purpose of the abbreviated procedure is to remove the "formidable barrier to market entry . . . that protects the brand name drug indefinitely from generic competition.").

under section 512(c)(2)(B) would be reasonably certain to be followed in practice. Although this drafting history is not definitive, it is consistent with FDA's interpretation.

Unlike Bayer’s interpretation, FDA’s interpretation does not hold animal generics to a higher standard of approval than brand name animal drugs. Section 512(c)(2)(A)(ii)’s first clause guarantees that an ANADA’s proposed *different* withdrawal period is just as safe as the withdrawal period previously approved for the RLNAD. Section 512(c)(2)(B) ensures that if an ANADA proposes a different withdrawal period from the RLNAD, the residues of the generic drug using that withdrawal period are consistent with the tolerances established for the RLNAD. Section 512(c)(2)(A)(ii) allows FDA to consider the additional safety element that the agency considered under section 512(d)(2)(D) as to the safety of the RLNAD’s withdrawal period for an ANADA’s different withdrawal period. In other words, FDA interprets the first clause of section 512(c)(2)(A)(ii) to play a role in ensuring that the withdrawal period for generic animal drugs is as safe as the withdrawal period for brand name animal drugs.

Fourth, the interpretation of section 512(c)(2)(A)(ii)’s first clause should be unique to animal drugs, because the provision has no counterpart in the human generics provisions. *See* FD&C Act § 505(j)(4)(B) (21 U.S.C. § 355(j)(4)(B) (containing equivalent language to section 512(c)(2)(A)(ii)’s second clause). The most obvious way that animal drugs are unique is that animal drugs given to food-producing animals can affect human food safety. *See* H. Rep. No. 100-972(II) at 14 (noting that GADPTRA “follows” the Hatch-Waxman Amendments “except in those respects where animal drugs should 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.”). Given that potential human food safety concerns distinguish animal drugs from human drugs, section 512(c)(2)(A)(ii)’s first clause, which has no equivalent in human generics provisions, is reasonably interpreted to pertain to human food safety. Unlike Bayer’s interpretation, FDA’s interpretation gives section 512(c)(2)(A)(ii)’s first clause a meaning that is unique to animal drugs and sensibly accounts for why the provision does not appear in the analogous human generics provisions.

Fifth, section 512(c)(2)(A)(ii)’s first clause should be read in light of how Congress used the provision’s language elsewhere in the FD&C Act. Congress first added language requiring that the conditions of use be reasonably certain to be followed in practice to sections 409(c)(3)(A) (21 U.S.C. § 348(c)(3)(A)) and 721(b)(5)(B) (21 U.S.C. § 379e(b)(5)(B)) in the 1962 Drug Amendments. *See* Pub. L. No. 87-781 (Oct. 10, 1962). The language was part of an exception to the Delaney Clause known as the “DES proviso” that permitted the approval of carcinogenic animal drugs for food-producing animals in certain circumstances.⁹ In the 1968

⁹ The DES proviso, which was enacted with diethylstilbestrol (DES) in mind, contained the following language: “[the Delaney Clause] shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended[.]” FD&C Act § 409(c)(3)(A) (emphasis added); *see also* FD&C Act § 721(b)(5)(B) (containing essentially identical language). This language, which was suggested by the Department of Health, Education and Welfare during consideration of the Color Additive Amendments in 1960, was intended to ensure that approved carcinogenic animal drugs would be safe for animals during their expected life cycle: “The condition that the additive must not adversely affect the animal is, of course, necessary, for, even in the absence of the anticancer proviso, the Food Additives Amendment requires that an additive for animal feed be safe for the animal, and under the basic provisions of the Food and Drug Act the product of a diseased animal is

Animal Drug Amendments, Congress added a third DES proviso to the new animal drug approval provisions. *See FD&C Act § 512(d)(1)(I) (21 U.S.C. § 360b(d)(1)(I)).* The Animal Drug Amendments also made the requirement that the conditions of use be reasonably certain to be followed in practice part of FDA's safety determination for all new animal drugs by creating section 512(d)(2)(D), which was based on section 409(c)(3)(A). *See, e.g., H. Rep. No. 90-875, at 5.* Both the text of section 512(d)(2)(D) and its legislative history confirm that Congress intended the provision to relate to safety determinations.¹⁰ Therefore, from its earliest appearance in the Act, the relevant language in sections 409(c)(3)(A), 721(b)(5)(B), 512(d)(1)(I), and 512(d)(2)(D), has pertained to safety.¹¹ Given that the relevant language relates to safety in sections 409(c)(2)(A), 721(b)(5)(B), 512(d)(1)(I), and 512(d)(2)(D), it is reasonable to interpret the first clause of section 512(c)(2)(A)(ii) to relate to safety as well. *See, e.g., Smith v. City of Jackson, Miss., 544 U.S. 228, 233 (2005)* ("[W]hen Congress uses the same language in two statutes having similar purposes . . . it is appropriate to presume that Congress intended that text to have the same meaning in both statutes"). Although section 512(c)(2)(A)(ii) does not contain an express reference to safety, to interpret the provision otherwise would be to ignore the broader statutory context and presume Congress had unprecedented, unexplained intentions here.

FDA's interpretation of section 512(c)(2)(A)(ii) is also more specifically supported by the agency's prior interpretations of the "conditions of use specified in proposed labeling and reasonably certain to be followed in practice" language in the DES provisos contained in sections 512(d)(1)(I), 409(c)(2)(A), and 721(b)(5)(B), in rulemakings implementing the DES provisos. *See 52 Fed. Reg. 49572, 49573 (December 31, 1987)* (describing the history of the DES proviso rulemaking proceedings); 21 CFR 500.80-500.92 (regulations implementing the DES provisos). Describing the regulations governing withdrawal periods in the 1979 proposed rule, the agency stated that "the withdrawal period must also be compatible with actual conditions of livestock management and reasonably certain to be followed in practice." 44 Fed. Reg. 17070, 17101 (March 20, 1979).

deemed adulterated." H. Rep. No. 1761, at 88 (1960) (letter from the Sec'y Health, Educ. and Welfare to Cong. Harris (May 13, 1960)).

¹⁰ An analysis by the Animal Health Institute submitted to Congress described section 512(d)(2)(D) as follows: "Clause (D) of new section 512(d)(2) is intended to give the Secretary added authority to consider safety questions in those instances where the prescribed conditions of use will not be followed." Animal Drug Amendments of 1968: Hearing on S. 1600 and H.R. 3639 Before the Subcomm. on Health of the S. Comm. on Labor and Pub. Welfare, 90th Cong. 79 (1968) (Attachment to statement of Luther Roehm, Immediate Past President, Animal Health Institute).

¹¹ Members of the Food and Drug Bar have recognized that 512(d)(2)(D) relates to safety determinations. *See Eugene I. Lambert, The Animal Drug Amendments of 1968: War Stories--A Comment on an Enactment*, 43 Food Drug Cosm. L.J. 781, 789 (1988) ("[I]n transposing the Delaney Clause into the Animal Drug Amendments, the requirement in the DES proviso that the conditions of use be reasonably certain to be followed in practice became a general requirement for determining the safety of animal drugs, rather than one limited to products seeking an exemption from the Delaney ban.").

The agency gave the following example of a withdrawal period that was not reasonably certain to be followed in practice: “For example, the use of a compound in lactating animals will not be approved if the required withdrawal time for milk exceeds 96 hours (4 days) because the management practices of milk production make observance of such discard times unlikely, or at least not reasonably certain to be followed in practice.” 44 Fed. Reg. 17070 at 17102. FDA interprets similar language in section 512(c)(2)(A)(ii) similarly.

Bayer asserts that section 512(c)(2)(A)(ii) is not intended to be limited to safety because, unlike section 512(d)(2)(D), it does not contain the term “safety.” See Bayer Supplement at 2-3. In addition to overlooking the legislative history of section 512(c)(2)(A)(ii) and related provisions, Bayer’s argument against interpreting the provision to relate to safety turns on a canon of construction that is inapt as applied to section 512(c)(2)(A)(ii) and section 512(d)(2)(D). Bayer cites *Burlington Northern & Santa Fe Ry. v. White*, 548 U.S. 53, 62-63 (2006), a case involving two provisions of Title VII of the 1964 Civil Rights Act, for the proposition that “where words differ . . . Congress acts intentionally and purposely in the disparate inclusion or exclusion.”). Bayer Supplement #2 at 9. The Supreme Court has emphasized that application of this canon depends on the statutory context. See *Field v Mans*, 516 U.S. 59, 75 (1995) (“the more apparently deliberate the contrast [between statutory provisions], the stronger the inference, as applied, for example, to contrasting statutory sections originally enacted simultaneously in relevant respects . . . the rule is weakest when it suggests results strangely at odds with other textual pointers[.]”); see also *Marx v. Gen. Revenue Corp.*, 133 S.Ct. 1166, 1175 (2013) (noting that the related principle of expressio unius est exclusio alterius does not apply “unless it is fair to suppose that Congress considered the unnamed possibility and meant to say no to it.”). Here, section 512(c)(2)(A)(ii) was enacted twenty years after section 512(c)(2)(D). FDA is not aware of (and Bayer has not cited) any legislative history suggesting that Congress in GADPTRRA intended to preclude FDA from construing section 512(c)(2)(A)(ii)’s first clause to pertain to safety. Moreover, application of the canon is not sensible here where other “textual pointers” in the FD&C Act, including sections 512(c), 512(d), 512(n), and provisions of AMDUCA, support FDA’s interpretation.

[REDACTED]

FDA rejects this argument because, as described above, section 512(c)(2)(A)(ii)’s first clause applies to ANADAs that propose different withdrawal periods from the RLNADs and thus were not previously approved by FDA. Section 512(c)(2)(A)(ii) is not superfluous because it applies to different withdrawal periods than section 512(d)(2)(D). The withdrawal periods subject to review under section 512(c)(2)(A)(ii)’s first clause are proposed by ANADA sponsors could not have been reviewed under section 512(d)(2)(D), because they were not previously approved for the RLNAD.

Finally, FDA’s interpretation leaves the carve-out provision untouched, does not confer unwarranted additional exclusivity to brand name animal drugs, and allows AMDUCA to apply to generics just as it does to their RLNADs. Bayer interprets the first clause of section 512(c)(2)(A)(ii) in a vacuum that ignores that clause’s relationship to the other provisions in the FD&C Act and GADPTRRA’s legislative history. Read in context, section 512(c)(2)(A)(ii)’s first

clause provides authority for disapproving ANADAs that pose safety concerns where an ANADA proposes a different withdrawal period from the RLNAD.

B. Bayer's citizen petition does not provide grounds to refuse to approve future ANADAs for enrofloxacin under section 512(c)(2)(A)(ii) of the FD&C Act.

Applying FDA's interpretation of section 512(c)(2)(A)(ii), Bayer has not provided the evidence necessary for FDA to grant the Petition. Bayer does not claim that future sponsors of generic enrofloxacin will propose withdrawal periods that are different from Baytril's. Nor does Bayer's evidence speak to this issue. Therefore, Bayer's Petition does not provide a basis for FDA to refuse to approve all future generic copies of Baytril under section 512(c)(2)(A)(ii) of the FD&C Act, as interpreted by FDA.

C. Even if GADPTRA were to impose an unconditional prohibition of ANADA approval based on the likelihood of extralabel use alone, Bayer fails to establish that likelihood.

Even if Bayer's interpretation of section 512(c)(2)(A)(ii) were correct, in order to grant the Petition, FDA would need to make an affirmative finding that the conditions of use prescribed, recommended, or suggested in the proposed labeling of any potential generic application of enrofloxacin 100 mg/mL are not reasonably certain to be followed in practice. In the absence of convincing evidence to the contrary, FDA has no basis to presume that veterinarians and end-users will break the law by ignoring FDA-approved labeling. *See Sigma-Tau Pharmaceuticals, Inc.*, 288 F.3d at 148 (rejecting the argument that foreseeable off-label use for a protected indication should bar approval of a generic drug, stating that "FDA is not obligated to assume bad faith"). In addition, FDA intends to ensure that the approved labeling of any generic enrofloxacin product clearly states that federal law prohibits its extralabel use in food-producing animals.

FDA makes drug approval decisions based on scientific evaluation, regardless of whether the drugs are intended for use in humans or animals. *See, e.g.*, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) ("Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of [a drug's] safety and effectiveness, but rather on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling."). FDA therefore analyzed whether the Petition or any of the subsequent submissions to the docket, including the Bayer Reply and its 390 appended exhibits, contain convincing evidence supporting a scientifically-based conclusion that "the conditions of use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice." After analyzing these materials, FDA determined that they did not support such a conclusion.¹²

¹² See July 8, 2013 Memorandum from L. Hungerford and V. Taylor to P. Jaensch; December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch; December 18, 2013 Memorandum (Memorandum II) from V. Taylor and L. Hungerford to P. Jaensch; December 19, 2013 Memorandum from C. Burnsteel and D. Benz to P. Jaensch; December 18, 2013 Memorandum from J. Bailey to P. Jaensch.

The Petition included the results of the Doane Cattle Vet Antibacterial Injectable Study (“cattle vet survey”) of 250 veterinarians and declarations from three veterinarians, Dr. Blood, Dr. Lechtenberg, and Dr. Lewis, in an effort to establish that a generic enrofloxacin product that is approved only for multiple-dose regimen is likely to be used for the unapproved single-dose regimen. Bayer made supplementary submissions to the docket on May 6, 2013 and September 12, 2013. In addition, on July 24, 2013, Bayer submitted a letter directing FDA’s attention to the July 19, 2013 Bayer Reply, which included 390 appended exhibits that were initially submitted as part of Bayer’s patent litigation against Norbrook. The 390 exhibits contained [REDACTED]

[REDACTED] Dr. Koontz, an agricultural economist, [REDACTED]

[REDACTED] Mr. Moyer, a retired veterinary pharmaceutical salesman, and [REDACTED]

¹³ The 390 exhibits also included [REDACTED]

[REDACTED] Norbrook made

submissions to the docket dated May 9, 2013, and May 16, 2013.

1. Bayer’s antibiotic use survey data do not support Bayer’s claims about the future use of a generic enrofloxacin.

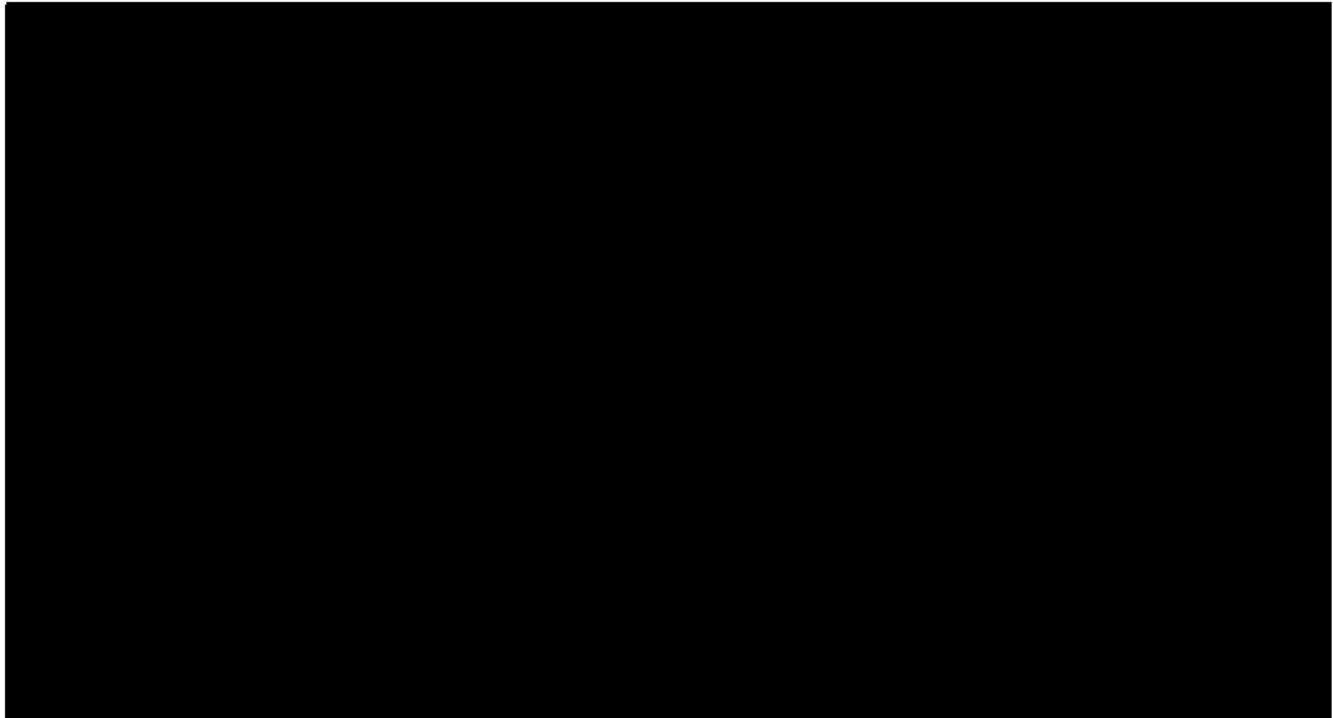
FDA concludes that the Doane cattle vet survey does not support Bayer’s assertion that “[i]t is reasonable to conclude that any generic approved for the Multiple-Day dosing regimen would likely be used as a Single-Dose.” Petition at 6. The Doane cattle vet survey was designed to answer a different question: how Baytril currently is being used, including the proportion of single versus multi-dose uses.¹⁴ To answer that question, Doane asked veterinarians about their current use of the two approved indications for Baytril in cattle, *i.e.*, the single-dose and the multiple-dose. To instead answer the question that Bayer deems relevant to this Petition, *i.e.*, whether respondents in the future would use a generic enrofloxacin product extralabelly in violation of the law, a different set of survey questions would need to be collected, using a valid sampling methodology. Significant expertise in survey research design and administration would be required to elicit valid responses regarding the likelihood that respondents would engage in future illegal behavior, as well as to assess hypothetical rather than actual practices. A substantial body of knowledge regarding the design of such surveys has emerged through research of issues such as substance abuse, HIV, and criminal behavior. The docket does not contain any such properly-designed survey. In addition, the survey included only veterinarians who currently use or dispense Baytril, a sample that does not necessarily represent the population that will use a generic version of Baytril in the future. There is no basis for extending the findings of the Doane survey to all potential future prescribers and users of a generic version of Baytril in cattle, as Bayer did. Moreover, no information was provided to show how well the

¹³ The 390 appended exhibits included several duplicate exhibits.

¹⁴ See July 8, 2013 Memorandum from L. Hungerford and V. Taylor to P. Jaensch.

respondents represented all Baytril users. Without that information, the validity of the survey results and the potential for biases could not be fully evaluated.¹⁵

Further, even if Doane's methodology were appropriate, Bayer's presentation of the survey results was insufficient to allow for comprehensive interpretation. For example, the range of variability and an estimate of the actual number of animals treated by the respondents were omitted, limiting the value of the survey results. Among survey respondents, while many veterinarians reported using Baytril for the approved single-dose regimen, a substantial group of veterinarians reported that they continue to use and recommend the multiple-dose regimen, notwithstanding the convenience and decreased cost described for the single-dose regimen.



2. **Bayer's economic analyses contain methodological flaws and fail to support Bayer's argument that end users will use a generic enrofloxacin extralabelly in violation of the law.**
- 

¹⁵ See *id.*

¹⁶ See December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

¹⁷ See *id.*

¹⁸ See *id.*

[REDACTED]

Bayer also provided expert reports from Dr. Koontz, which analyzed the costs of the single-dose and multiple-dose treatments and used rational choice theory to conclude that cattlemen will use Norbrook's product extralabelly in violation of the law. Bayer Reply Ex. 161,

[REDACTED] Rational choice theory is not widely accepted as a model for health decision-making because it ignores effects of other factors such as relevant social norms and decision makers' perceived power. In his report, Dr. Koontz failed to consider other factors that influence such decision-making.

[REDACTED] which shows that Dr. Koontz's prediction about how end users will behave is inconsistent with [REDACTED]

3. [REDACTED]

[REDACTED]

[REDACTED] FDA has carefully evaluated the safety of enrofloxacin with regard to its microbiological effect on bacteria of human health concern and concluded that approved uses do not impact public health.

¹⁹ FDA uses the term "effects" as a statistical term that applies to all analyzed variables in the unpublished Bayer field trial, including the number of animal relapses (1st, 2nd, chronic), mortality at day 28 and 60, average daily gain at day 28, and total treatment days.

²⁰ See December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

4.

[REDACTED]
[REDACTED] was not supported by evidence in the docket.

[REDACTED]

[REDACTED] Cattle should be handled calmly and purposefully. If cattle are handled properly, the multi-dose treatment does not raise additional safety concerns for handlers or cattle.²¹

FDA does not have evidence to conclude that the multi-dose treatment is not an appropriate method for treating BRD with enrofloxacin.

[REDACTED]

²² We note that despite Bayer's criticisms of the multi-dose treatment, Bayer continues to include the multi-dose claim on its label for Baytril.

5.

[REDACTED] does not support a finding that veterinarians and end-users will use a generic enrofloxacin in an illegal extralabel manner.

²¹ See December 19, 2013 Memorandum from C. Burnsteel and D. Benz to P. Jaensch.

²² See *id.*

²³ See *id.*

The declarations from Dr. Blood, Dr. Lechtenberg, and Dr. Lewis attached to the petition, and the [REDACTED]

[REDACTED] did not provide scientific evidence from which FDA reasonably may conclude that veterinarians would engage in an illegal use of generic enrofloxacin for the single-dose regimen. Opinions, even when given by experts, are considered the least robust form of evidence in scientific evaluation, and that reports from respondents about the hypothetical behavior of an unspecified group of other individuals constitute anecdotal rather than scientific evidence.²⁴ Bayer's experts offered opinions about the economic and practical incentives for using a single-dose product rather than a product approved only for a multiple-dose regimen, but they had not provided evidence to support their assumption that such incentives would lead users to engage in unlawful extralabel use. In addition, Dr. Blood, Dr. Lechtenberg, and Dr. Lewis had not taken into account measures that existed in 2006 to control extralabel use of antimicrobial drug products, including procedures for applying AMDUCA, FDA's 1997 prohibition of extralabel use of fluoroquinolones, and Beef Quality Assurance (BQA) programs. FDA has implemented measures, post-2006, to control extralabel use of certain antibiotics, including a recent prohibition on extralabel use of cephalosporins, which had involved the participation of many veterinarians, producers, industry, and the public. Therefore, the declarations of Dr. Blood, Dr. Lechtenberg, and Dr. Lewis do not provide scientific evidence from which FDA reasonably may conclude that veterinarians would engage in an illegal use of generic enrofloxacin.

[REDACTED]

²⁴ See July 8, 2013 Memorandum from L. Hungerford and V. Taylor to P. Jaensch; December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

²⁵ See December 19, 2013 Memorandum from C. Burnsteel and D. Benz to P. Jaensch.

²⁶ See December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

6. [REDACTED]

[REDACTED] This argument of Bayer's is not convincing. As [REDACTED]

[REDACTED] It is reasonable to expect that Norbrook used the more stringent endotoxin limit to avoid the need to submit a post-approval supplement to update its endotoxin limit after the single-dose treatment came off patent in the United States.³¹

²⁷ See December 19, 2013 Memorandum from C. Burnsteel and D. Benz to P. Jaensch; December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

²⁸ See December 19, 2013 Memorandum from C. Burnsteel and D. Benz to P. Jaensch.

²⁹ See December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

³⁰ See December 18, 2013 Memorandum from J. Bailey to P. Jaensch. [REDACTED]

[REDACTED] FDA regulations contain no such requirement. FDA's "Guidance for Industry, 'Pyrogen and Endotoxins Testing: Questions and Answers'" refers to U.S. Pharmacopeial Convention (USP) for the appropriate way to calculate the endotoxin limit. Nothing in FDA's guidance document or the USP prohibits a sponsor from establishing a tighter endotoxin limit than a product's maximum dose would allow.

³¹ See December 18, 2013 Memorandum from J. Bailey to P. Jaensch.

In addition, [REDACTED]

[REDACTED] FDA concluded during review of the Norbrook ANADA that the sponsor performed appropriate broaching studies to correspond to a multi-day treatment schedule for its generic enrofloxacin.

7. [REDACTED]
[REDACTED]

[REDACTED] anecdotal opinions, even when given by experts, are considered the least robust of evidence in scientific evaluation. Bayer presented no data to assess what end users will do. In the absence of such data, anecdotal opinion evidence [REDACTED] do not support a finding that the labeled conditions of use of a generic enrofloxacin are not reasonably certain to be followed in practice and that veterinarians and producers will use a generic enrofloxacin product extralabelly in violation of the law.³² [REDACTED]
[REDACTED]

8. Additional submissions to the docket by Bayer and Norbrook did not contain data regarding the likelihood of extralabel use.

None of the subsequent submissions to the docket included data upon which FDA could rely in making a scientifically based assessment of the likelihood of extralabel use. For example, Bayer's May 6, 2013, submission alleged that Norbrook representatives had encouraged off-label use, but provided no data to support this claim. Bayer's September 12, 2013 supplemental submission referred to the same survey results and expert reports analyzed above.³⁴ Neither of Norbrook's submissions, dated May 9, 2013, and May 16, 2013, included data regarding the likelihood of extralabel use.

In conclusion, neither the Petition nor the subsequent submissions to the docket provide evidence from which FDA could reach a scientifically-based conclusion that the conditions of

³² See December 18, 2013 Memorandum (Memorandum I) from L. Hungerford and V. Taylor to P. Jaensch.

[REDACTED]

³⁴ See December 18, 2013 Memorandum (Memorandum II) from V. Taylor and L. Hungerford to P. Jaensch.

use prescribed, recommended, or suggested in the proposed labeling are not reasonably certain to be followed in practice. FDA finds that the materials in the docket do not support Bayer's requested action, namely the denial of all ANADAs for enrofloxacin 100 mg/mL injectable solution under section 512(c)(2)(A)(ii) of the Act.

D. Bayer's post-approval monitoring and controlled distribution system

Bayer's argument that there is little guarantee that other companies will implement a post-approval monitoring program and controlled distribution system similar to those implemented by Bayer does not provide a sufficient ground under the FD&C Act to deny any and all ANADAs for enrofloxacin 100 mg/mL injectable solution. On February 2, 2001, FDA concluded that Bayer's post-approval monitoring program had provided adequate data regarding antimicrobial resistance and was no longer necessary. Since then, susceptibility of bacteria to Baytril has been monitored through the National Antimicrobial Resistance Monitoring System and other sources of information. FDA has no reason to believe and Bayer has offered no evidence to support an argument that additional monitoring would be necessary for generic versions of Baytril.

V. Conclusion

When viewed in the context of the entire statute and legislative history, it is clear that Bayer's interpretation of section 512(c)(2)(A)(ii) is untenable. The first clause of section 512(c)(2)(A)(ii) is properly interpreted to allow FDA to disapprove a generic application proposing a different withdrawal period from its RLNAD where the proposed different withdrawal period is not reasonably certain to be followed in practice, raising a human food safety concern. However, even if Bayer's interpretation were accepted, Bayer did not provide FDA with a sufficient scientific basis to support a decision to refrain from approving all future ANADAs for copies of Baytril under section 512(c)(2)(A)(ii). Therefore, FDA denies the Petition.

Sincerely,



Michael R. Taylor
Deputy Commissioner for Foods and Veterinary Medicine

cc: HFA-305 (Docket FDA-2006-P-0010)