

February 26, 2020

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Re: Comment to Guidance for Industry #256: Compounding Animal Drugs
from Bulk Drug Substances (FDA-2018-D-4533)**

To Whom It May Concern:

We write on behalf of a coalition of pharmacies specializing in the compounding of medication for animal health. These pharmacies, and many others like them around the country, will be negatively impacted by the proposed guidance set forth in the draft Guidance for Industry #256: Compounding Animal Drugs from Bulk Drug Substances (“GFI #256”). Accordingly, we submit the below comments in the hopes that FDA’s Center for Veterinary Medicine (“CVM”) will reconsider the proposed path set forth in GFI #256 and find a regulatory scheme that works best for all industry stakeholders. Our request is predicated upon the following:

- **FDA has no authority to regulate veterinary compounding.** Veterinary compounding is not subject to The Federal Food, Drug & Cosmetic Act (“FDCA”). The FDCA was designed to regulate drug manufacturers, not veterinary compounders. Likewise, FDA cannot find its authority in the provisions of The Animal Medicinal Drug Use Clarification Act of 1994 (“AMDUCA”) as AMDUCA has nothing to do with, and sets forth no restrictions on, veterinary compounding. Finally, to the extent that FDA is attempting to extend Sections 503A and 503B to veterinary compounding, as acknowledged by FDA, Sections 503A and Sections 503B of the FDCA do not apply to animal drugs and, accordingly, FDA cannot simply create equivalent provisions for veterinary compounding via a guidance document.
- **FDA is practicing medicine by attempting to regulate the practice of veterinary medicine.** As apparent from GFI #256, FDA is infringing on the medical judgment of veterinarians by: (1) limiting veterinarian access to medications compounded for patient compliance by calling these medications “copies” and requiring a “medical rationale” in order to prescribe them; and (2) determining if a commercially available medication can treat a disease, and ONLY if not, allowing the medication to be compounded from bulk. Decisions with regard to how best to treat an animal patient should only be made by a practitioner. FDA cannot conflate its own judgment with that of the veterinary medical profession.

- **The regulatory scheme set forth in GFI #256 will have a severely negative impact on animal health.** GFI #256 must be withdrawn because (1) it supports, without justification, starting compounding with FDA-approved human and animal drugs rather than bulk active pharmaceutical ingredients, which is known to decrease quality and increase risk, and expose animal patients to unnecessary and even dangerous ingredients; and (2) it will essentially eliminate the ability to use bulk substances to prepare compounded animal medication for office use, and office use is a vital and necessary component in the practice of veterinary medicine; and (3) it will increase the costs of critical compounded medication to such an extent that animal patients will be forced to go without medical care. Veterinary compounders employ over 40,000 formulations in their practices to treat animal patients nationwide because FDA-approved medications are unavailable or unsuitable to meet the unique needs of animal patients on the prescriptive authority of veterinarians. The need for such an enormous variety of formulations cannot be addressed by commercially available drugs or by the limited situation under which GFI #256 permits compounding from bulk drug substances. If veterinary compounders were limited in the manner prescribed by GFI #256, veterinarians and animal caregivers would not obtain the medication they need to care for animals, causing unnecessary suffering and, potentially, death.

Accordingly, for the reasons set forth in greater detail below, we respectfully request that FDA withdraw GFI #256 and that CVM engage in further dialogue with members of this coalition, as well as other industry stakeholders, on the best path forward for veterinary compounding. We understand that CVM did not meet with veterinary compounding pharmacies who provide medications for animals to discuss the implications of CVM's policies on animal health prior to issuing the draft. To that end, we respectfully request a formal meeting with CVM leadership to discuss our concerns with GFI #256 and its implications on the treatment of animals in greater detail.

1. FDA Has No Authority To Take The Positions Outlined in GFI #256.

Despite the many comments submitted in response to the previous iteration of this guidance, GFI #230, FDA mistakenly continues to assert that it has authority to regulate veterinary compounding. As set forth below, FDA does not have the authority to regulate compounded drugs for animal use.

FDA in GFI #256, incorrectly, asserts that all compounded animal drugs are "new drugs" and as such, subject to FDA control. FDA asserts that any animal drug must be either (1) approved by FDA through the new animal drug approval process; (2) conditionally approved pursuant to Section 571 of the FDCA; or (3) indexed under Section 572 of the FDCA. To the extent that the FDCA permits the compounding of animal drugs without going through one of the three pathways, FDA believes it does so only via AMDUCA and its corresponding regulation, 21 CFR 530.13. *See* GFI #256 at pp. 6-7. Per FDA, compounding animal drugs from bulk drug substances is animal drug manufacturing and is not permitted by the FDCA. *Id.* at p.6. Nevertheless, FDA recognizes that manufactured animal drugs are not always suitable for treatment. As such, FDA presents us with GFI #256 as a way to permit the compounding of animal drugs using bulk drug substances under certain circumstances to meet treatment needs. *See* GFI #256 pp. 7-9.

FDA's entire premise for GFI #256 is unfounded. What FDA is essentially creating in GFI #256 is a two-track federal regime to regulate veterinary compounding: (1) compounding from human or animal approved drugs subject to the extralabel use provisions in AMDUCA and in 21 C.F.R. 530; and (2) compounding from bulk ingredients subject to the restrictions set forth in GFI #256. FDA has no authority to create this two-track regime under the FDCA. First, veterinary compounding is not subject to the FDCA. The FDCA was designed to regulate drug manufacturers, *not* veterinary compounders. Likewise, FDA cannot find its authority in the provisions of AMDUCA as it has nothing to do with, and sets forth no restrictions on, veterinary compounding. Finally, with regard to GFI #256's attempt to extend the framework set forth in Sections 503A and 503B to veterinary compounding, as acknowledged by FDA, Sections 503A and Sections 503B of the FDCA do not apply to animal drugs and, accordingly, FDA cannot simply create equivalent provisions for veterinary compounding via a guidance document. For these reasons, GFI #256 must, therefore, be withdrawn.

(a) Veterinary Compounding Is Not Subject To The FDCA.

The FDCA gives FDA the authority to regulate drug manufacturing, not veterinary compounding. Veterinary compounding has been historically regulated by the States as a traditional part of the practice of pharmacy. There have been no amendments to the FDCA to allow FDA to regulate veterinary compounding.

As FDA is no doubt aware, veterinary compounding is expressly recognized and highly regulated by State laws, and is a widespread practice performed by licensed pharmacy professionals and veterinarians throughout the country. Well before passage of the FDCA, over eight decades ago, States regulated compounding as part of their oversight of the practice of pharmacy. Since the passage of the FDCA in 1938, veterinary compounding has continued to be regulated by the States. In turn, since at least 1992, FDA, Congress, and the United States Supreme Court have consistently reaffirmed that FDA does not have the authority to regulate traditional compounding activities, like compounding for animals, or to subject those activities to the FDCA.

Nothing has changed with respect to this State and federal balance over veterinary compounding in the 82 years since the FDCA was enacted; and no new laws have been passed to expand FDA's authority over the State-regulated practice of veterinary compounding. Nevertheless, in a bid to assert authority over yet another vestige of the nation's healthcare regime, FDA rests its authority to regulate veterinary compounding in FDCA's expansive definition of "new drug." See GFI #256 at p. 3. The legislative history of the FDCA, however, clearly supports the view that *drug manufacturing*, not drug compounding, was the intended target of the FDCA's drug approval scheme.

When it enacted the FDCA in 1938, Congress was reacting in response to a national outcry over recent deaths involving manufactured drugs and was focused on the fact that drug manufacturing was conducted by unlicensed, unregulated nonprofessionals. In contrast, the practice of pharmacy and, accordingly, the practice of compounding medication, was already heavily regulated by State laws. Congress' focus on unlicensed large-scale manufacturing, and not on the licensed practice of pharmacy, demonstrates that Congress did not intend to subject all drugs compounded and dispensed by licensed professionals to the same regulatory scheme as drugs manufactured by unlicensed manufacturers.

Congress' desire to regulate drug manufacturing, and not compounding, is all the more obvious when one considers that the FDCA's structure is an extremely poor fit for compounded animal medications. The FDCA prohibits the introduction or delivery for introduction into interstate commerce of "new drugs" unless, among other things, an application is filed that includes "a full list of the articles used as components of such drug," 21 U.S.C. §§ 360b(a)(1), (b)(1)(B), as well as "full reports of investigations." *Id.* § 360b(b)(1)(A). FDA has long interpreted this to mean that new drugs must be subjected to extensive testing and well-controlled clinical studies to determine their safety and effectiveness. Compounded medications by their very nature, however, often have unique components and are prepared to address specific, limited issues. Accordingly, compounded medications are ill-suited for clinical studies and, rather, are subject to separate standards designed to ensure the proper preparation of compounded medications.

Given this history and context, Congress could not have intended to subject pharmacy-compounded drugs to the lengthy and expensive new animal drug approval process simply by enacting a broad definition of "new drug." Said differently, Congress did not hide the elephant of FDA regulation of all compounded drugs in the mousehole of the FDCA's definition of "new drug." Courts that have addressed the issue also have recognized that the FDCA's new drug approval process is an especially poor fit for regulating pharmacy compounding; and would potentially eradicate compounding despite the recognized importance, historical acceptance, and decades-long State regulation of the practice. *See, e.g., Thompson v. Western States Med Ctr.*, 535 U.S. 357, 369-70 (2002); *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 398 (5th Cir. 2008).

The well-established rule of lenity also demonstrates that GFI #256 is unlawful. The FDCA provides for both criminal and civil penalties for any prohibited acts under 21 USC § 331. Accordingly, the rule of lenity means that FDA cannot construe the term "new drug" to criminalize more conduct than that which Congress intended to criminalize under the FDCA. But, that is exactly what FDA does in GFI #256 by declaring that unless an animal drug is compounded from bulk substances in accordance with GFI #256, the compounded drug will be considered unsafe and adulterated under the FDCA. In that same vein, FDA's construction of "new drug" is improper because FDA has never disputed that veterinary compounding from bulk ingredients is a traditional component of pharmacy practice regulated under State laws and regulations. Nonetheless, via GFI #256, FDA attempts to upset the expectations of pharmacies and veterinarians—which FDA helped to create through decades of acknowledging that veterinary compounding is regulated primarily by the States—by unilaterally expanding its authority under the FDCA, negatively impacting the federal-State balance on traditional compounding, and potentially subjecting many State-licensed veterinarians and pharmacists to criminal liability. This is improper.¹

¹ FDA's declaration of what is and is not illegal under the scheme set forth in GFI #256 also puts compounding pharmacies at significant risk. Compounding pharmacies are now apparently subject to the whole gamut of FDA enforcement powers if they do not comply with GFI #256. This means that FDA could, according to GFI #256, seize all of a compounding pharmacy's drug products and active pharmaceutical ingredients simply because, for example, a veterinarian fails to make a legal determination that no FDA-approved, conditionally approved, or indexed drugs are available to treat an animal. GFI #256 at p. 7. These and other related enforcement actions would put compounding pharmacies at the mercy of FDA based solely on FDA's "current thinking" as established in a purportedly nonbinding guidance document. FDA does not have the authority, in the FDCA or otherwise, to impose this type of regulatory regime.

Enacting the GFI would also effectively allow FDA to preempt State pharmacy and veterinary laws relating to veterinary compounding. Federal preemption is only proper, however, where a statute contains an express preemption provision, there is clear evidence that Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of federal authority under a federal statute. Executive Order No. 13132, 64 Fed. Reg. 43, 255 (Aug. 4, 1999); Executive Memorandum on Preemption, 74 Fed. Reg. 24693, 24693–94 (May 20, 2009); *see also Wyeth v. Levine*, 555 U.S. 555, 565 (2009) (“[I]n all pre-emption cases, and particularly in those in which Congress has legislated . . . in a field which the States have traditionally occupied . . . we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress,” (internal citations omitted)); *Altria Group v. Good*, 555 U.S. 70, 77 (2008) (“When addressing questions of express or implied pre-emption, we begin our analysis ‘with the assumption that the historic police powers of the States [are] not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.’”). Congress has not expressed through the FDCA any intent, express or implied, to preempt State veterinary compounding laws.

In sum, if Congress wanted to give FDA the power to regulate all veterinary compounding, it would have said so. It did not, and it has instead remained silent on the issue of FDA’s authority over veterinary compounding. This silence does not give FDA the authority to declare that all veterinary compounding is *per se* manufacturing and subject to the FDCA. FDA cannot take over the State-regulated practice of veterinary compounding absent statutory authority, and it cannot, in GFI #256, revise, extend, and re-interpret the FDCA. The entire purported legal basis for the GFI is therefore false.

(b) FDA Is Wrong To Rely On AMDUCA As The Basis For Its Authority to Regulate Veterinary Compounding.

Notwithstanding the fact that FDA has no authority whatsoever via the FDCA to regulate veterinary compounding, FDA appears to ground its alleged authority to regulate veterinary compounding from bulk substances via AMDUCA. FDA is, again, wrong.

AMDUCA permits veterinarians to prescribe extralabel uses of certain approved new animal drugs and approved human drugs for animals under certain conditions. Extralabel use refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. Under AMDUCA and its implementing regulations published at 21 CFR §§ 530, *et seq.*, any extralabel use of an approved new animal or human drug must be by or on the lawful order of a veterinarian within the context of a veterinarian-client-patient relationship (a “VCPR”). In other words, AMDUCA simply permits certain off-label uses of FDA-approved human and animal drugs in the treatment of animals, and authorizes FDA to promulgate regulations which “establish the conditions” under which veterinarians may prescribe off-label use of FDA-approved drug products. *See* 21 U.S.C. §§ 360b(a)(4) and (a)(5). AMDUCA makes no reference whatsoever to veterinary compounding generally or veterinary compounding from bulk ingredients, and it does not purport to prohibit veterinary compounding from bulk ingredients or confer any authority onto FDA to regulate all veterinary compounding from bulk ingredients. If Congress intended for AMDUCA to cloak FDA with the authority to displace the States as regulators of veterinary compounding from bulk ingredients, it would not have hidden that grant of authority in a provision relating

to the off-label uses of animal drugs and without any reference of any kind to compounding. *See, e.g., Whitman v. American Trucking Assns., Inc.*, 531 U.S. 457, 468 (2001) (“Congress, we have held, does not alter the fundamental details of a regulatory scheme in vague terms or ancillary provisions—it does not, one might say, hide elephants in mouseholes”); *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 160 (2000) (“[W]e are confident that Congress could not have intended to delegate a decision of such economic and political significance to an agency in so cryptic a fashion”).

Nevertheless, FDA has chosen to hang its hat on a threadbare assertion of authority by way of AMDUCA. To be clear, extralabel use is *not* compounding. Compounding is the traditional practice of mixing and preparing a drug compound comprised of one or more active ingredients pursuant to a prescription. “Extralabel use,” on the other hand, is defined as:

Actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses.

21 CFR 530.3(a). This definition makes no reference to compounding. Nor can it, as compounded medication inherently has no approved label and, accordingly, cannot be “used” in a manner that is inconsistent with that label. Extralabel use and compounding have absolutely no relation to one another and, accordingly, FDA’s attempt to ground its authority to regulate veterinary compounding in the extralabel use provisions of AMDUCA makes no sense. *See Wyeth v. Levine*, 555 U.S. 555, 588 (2009) (“[A]n agency literally has no power to act, let alone pre-empt the validly enacted legislation of a sovereign State, unless and until Congress confers power upon it,” (internal citations omitted)); *see also Ry. Labor Executives’ Ass’n v. Nat’l Mediation Bd.*, 29 F.3d 655, 670 (D.C. Cir. 1994) (“Unable to link its assertion of authority to any statutory provision, the [Agency’s] position in this case amounts to the bare suggestion that it possesses plenary authority to act within a given area simply because Congress has endowed it with some authority to act in that area. We categorically reject that suggestion. Agencies owe their capacity to act to the delegation of authority, either express or implied, from the legislature.”).

FDA’s regulations promulgated pursuant to AMDUCA, 21 C.F.R. § 530.13(a), also do not give FDA the authority it seeks. Section 530.13 explicitly references both compounding and compounding from bulk, even though AMDUCA made no mention of either. As previously stated, moreover, FDCA does not provide FDA with authority to regulate veterinary compounding. Thus, FDA is not authorized by AMDUCA to restrict compounding from bulk via Section 530.13. Moreover, and despite FDA’s reference to bulk drugs in Section 530.13, it does not purport to regulate the practice of compounding and instead refers parties to FDA’s non-binding guidance documents on the subject. *See id.* § 530.13(c). Accordingly, neither AMDUCA nor Section 530.13 give FDA the authority it seeks to implement GFI #256.

(c) FDA Does Not Have The Authority To Extend The Section 503A And 503B Exemptions To Veterinary Compounding.

Finally, GFI #256 is also a blatant attempt to extend Sections 503A and 503B exemptions to veterinary compounding from bulk ingredients.² See GFI #256 at 9, imposing the prescription requirements of Section 503A, and a hybrid of the Section 503A bulk ingredient requirements, onto pharmacies compounding animal drugs; GFI #256 at 11, imposing similar bulks list requirements applicable to Section 503B outsourcing facilities to compounded animal drugs. Guidance documents cannot be used by FDA to create new authority for itself or to impose an entirely new legislative framework for veterinary compounding, without a statutory framework passed by Congress and signed by the President. See Memorandum from the Attorney General, *Prohibition on Improper Guidance Documents*, Nov. 16, 2017 (“[G]uidance [documents] may not be used as a substitute for rulemaking and may not be used to impose new requirements on entities outside the Executive Branch. Nor should guidance [documents] create binding standards by which the Department will determine compliance with existing regulatory or statutory requirements.”); see also *Brown & Williamson Tobacco Corp. v. Food & Drug Admin.*, 153 F.3d 155, 176 (4th Cir. 1998), *aff’d*, 529 U.S. 120 (2000) (“As the Supreme Court has previously stated about a different agency and its enabling statute, neither federal agencies nor the courts can substitute their policy judgments for those of Congress.”). Guidance documents are instead to be used to interpret, explain, or define existing regulations and existing statutory authority. There are no such regulations or statutes with respect to FDA’s authority over veterinary compounding, and FDA cannot create these statutes and regulations through a purportedly nonbinding guidance document.

FDA’s attempt to legislate through a guidance document is also directly contrary to the plain language of The Drug Quality and Security Act (“DQSA”) and FDA’s own irrefutable and recorded positions on the issue. The DQSA has nothing to do with veterinary compounding. It explicitly applies solely to compounded human drugs, DQSA, p. 1 (“An Act to amend the Federal Food, Drug, and Cosmetic Act [FDCA] with respect to human drug compounding”), and was enacted solely with human drug compounding in mind. FDA has conceded this fact when it states that “Section 503A and 503B of the FD&C Act (21 U.S.C. § § 353a, 353b), which provide statutory exemptions for compounded human drugs, do not apply to drugs compounded for use in animals.” See GFI #256 at fn. 11. FDA therefore cannot extend the DQSA to veterinary compounding by way of a guidance document.

FDA has also repeatedly affirmed that the FDCA’s provisions relating to human drug compounding do not apply to animal drugs. For example, in federal court filings, FDA explained that “[t]here is no statutory basis for extending the human drug compounding exemptions of FDAMA to animal drugs because Congress enacted distinct exemption schemes for compounding human and animal drugs.” *United States v. Franck’s et al.*, Case No. 5:10-cv- 00147-TJC-TBS, Dkt. No. 54, FDA’s Mot. for Summ. J. at 16 (M.D. Fla. Dec. 13, 2010).

In various guidance documents implementing the DQSA, FDA unambiguously advised the industry that facilities *only* compounding animal drugs should not register as outsourcing facilities. In its

² Director Eric Nelson indicated when FDA states “federal facilities (i.e., facilities operated by the Federal government),” in GFI #256, it does NOT include or implicate any animal compounding done in outsourcing facilities registered with FDA under Section 503B.

final guidance for entities considering registering as an outsourcing facility under Section 503B, FDA unambiguously states that “you should not register a facility as an outsourcing facility if the only activities conducted at the facility are ... compounding ... animal drugs ... because none of the products produced at the facility would qualify for the exemptions provided in section 503B.” FDA Final Guidance, For Entities Considering Whether to Register As Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act, p. 4 (Aug. 2015). In its guidance concerning implementation of Section 503A, FDA unambiguously states that “Section 503A also does not apply to drugs intended for use in animals. The statutory and regulatory provisions governing the compounding of human drug products differ from those governing the compounding of animal drug products.” FDA Guidance, Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act, p. 2 n. 3 (June 2016). It is outrageous for FDA to now reverse course in light of these repeated and unambiguous statements and to, without explanation and through a purportedly nonbinding GFI, transpose the limitations of Sections 503A and 503B onto veterinary compounding.

FDA also has no authority to propose a positive list for veterinary compounding akin to Section 503B’s bulks positive list. *See* GFI #256 at Appendix. FDA does not have the power through FDCA to create a list of bulk ingredients that pharmacies can use for compounded animal medication. Unlike Section 503B of the FDCA, there is nothing in the FDCA that specifically provides for a bulks list in order for veterinary compounders to compound medications using bulk substances for office use.

Therefore, as FDA has no authority to regulate veterinary compounding in the manner set forth in GFI #256, the guidance must be immediately withdrawn.

2. FDA Does Not Have The Authority To Regulate The Practice Of Veterinary Medicine Via GFI #256.

Not only does FDA lack authority to regulate veterinary compounding, also it has no authority to regulate the practice of veterinary medicine. And yet, as set forth in GFI #256, FDA replacing its own judgment for that of veterinarians by: (1) limiting veterinarian access to medications compounded for patient compliance (adding flavoring) by calling these medications “copies” and requiring a “medical rationale” in order to prescribe them; and (2) determining if a commercially available medication can treat a disease, and ONLY if not, allowing the medication to be compounded from bulk. Decisions with regard to how best to treat an animal patient should only be made by a practitioner. FDA cannot conflate its own judgment with that of the veterinary medical profession.

As a threshold matter, the practice of veterinary medicine, like the practice of pharmacy, is regulated by the States. When Congress enacted the FDCA in 1938, it intended to preserve practitioners’ right to use compounded medications. Since that time, Congress has not passed any law giving FDA the authority to propose any regulatory scheme for veterinarians’ prescribing or compounding animal drugs, let alone the comprehensive new regime set forth in GFI #256. Accordingly, the practice of veterinary medicine is beyond the power of FDA and is instead within the purview of the States. *See, e.g., Linder v. United States*, 268 U.S. 5, 19 (1925); *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1496 (D.C. Cir. 1996); *United States v. Kaplan*, 2014 U.S. Dist. LEXIS 124176, *21–22 (D. Nev. July 9, 2014). GFI #256 blatantly violates this principle.

GFI #256 requires veterinarians to justify, in writing, the need to compound medication using bulk substances under certain circumstances by documenting the “medical rationale” for the compounded medication in the prescription or, if the veterinarian is compounding the drug, in the patient’s medical record. GFI #256 at p. 10. FDA, in other words, appears intent on controlling veterinarians’ medical judgment by requiring them to use compounded medications only in certain, limited circumstances, and by requiring the veterinarians to justify their treatment recommendations before prescribing a compounded medication. These requirements could permit FDA to second-guess a veterinarian’s medical judgment and to initiate an enforcement action against the veterinarian if FDA disagrees with the veterinarian’s medical determinations as to the medical rationale for compounded medications. FDA does not have the authority to control State-licensed veterinarians’ medical decisions in this way.

Indeed, even if FDA has the authority to regulate veterinary compounding in the manner set forth in GFI #256, FDA fails to appropriately explain how it intends to enforce that guidance. For example, as previously stated, GFI #256 requires that a medical rationale be documented on the patient-specific prescription (or if the veterinarian is compounding the medication, in the patient’s medical record) when a veterinarian prescribes a compounded medication that meets the very broad definition of a copy of a marketed FDA-approved drug. *See* GFI #256 at p. 9-10. Criteria that would qualify a compounded preparation as a “copy” includes compounded preparations that contain the same API, in a same, similar, or easily substitutable strength, and given by the same route of administration as an FDA-approved drug. *Id.* In other words, compounds that differ from marketed FDA-approved drugs in flavor, oral dosage forms, topical dosage forms, or some unknown range of strength, will require a medical justification. It is not known, however, how FDA will determine a medical justification to be sufficient or adequate. Moreover, since both human and veterinary FDA-approved drugs are factors in determining whether something is a copy, veterinarians will now need to be knowledgeable of FDA-approved drugs on the market for human use in order to provide a potential medical justification for why a compounded veterinary version is necessary to treat an animal patient. FDA on the one hand appears to impose additional burdens on veterinarians but, even if those burdens are met, may still second guess a veterinarian’s judgment.

Second, GFI #256 intrudes on the State-regulated practice of veterinary medicine because FDA—not the practitioner—determines if the animal should be treated with the commercially available drug before allowing a bulk substance to be used to compound medication for office use. GFI #256 at pp. 11-12. Most States have specific provisions in their regulations allowing veterinarians to order compounded medication for office use, and allowing compounding pharmacies to compound animal drugs for ‘veterinarians’ office use. Indeed, it is uniquely important for veterinarians to have access to office-use medications because veterinary clinics often act as emergency rooms and hospitals for animals. GFI #256 directly obstructs or contradicts these traditional veterinary practices which are permitted under State law.

For example, GFI #256 permits the compounding of animal drugs from bulk substances as office use only if a specific set of criteria are met, one of which is that the drug is compounded only from a drug substance listed on FDA’s “List of Bulk Drug Substances for Compounding Office Use Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals” (the “List”). GFI #256 at pp. 11-12. Drug substances are only eligible for inclusion on the List if, among other things:

1. There is no marketed FDA-approved, conditionally approved, or indexed animal drug that can be used as labeled to treat the conditions;
2. There is no marketed FDA-approved animal or human drug that could be used in an extralabel manner under section 512(a)(4) or (a)(5) of the FD&C Act and 21 CFR part 530 to treat the condition;
3. The drug cannot be compounded from a marketed FDA-approved animal or human drug consistent with 21 CFR part 530; and
4. Immediate treatment with the compounded drug is necessary to avoid animal suffering or death.

GFI #256 at Appendix. These criteria limit the availability of office use medication thereby restricting veterinarians' judgment as to the best compounded medication needed to treat their animal patients. Instead, through the use of these criteria, and the requirement that the industry essentially prove each and every bulk drug substances' eligibility for inclusion on the List, FDA is usurping the judgment of veterinarians. FDA is making medical determinations about the best method of treatment for animal patients and what substances are best for animal patients. FDA is not qualified to make these judgments, nor does it have any authority to do so by way of FDCA or other statute.

Nonetheless, FDA has already taken steps to exercise its unqualified judgement with regard to bulk substances through positive and negative bulks lists.³ For example, FDA will not allow the use of Doxycycline to compound medication for veterinary office use for emergency antibiotic treatment and for circumstances involving renal failure because, in FDA's opinion, FDA-approved products can be "combined to reach an appropriate dose concentration by directly administering the tablets or capsules, or used to compound a powder or suspension for oral administration." Compounded Doxycycline is most veterinarians' first line of defense for the treatment of small animals, like small-size dogs and cats, puppies and kittens. Liquid compounded Doxycycline, in particular, is essential for the treatment of small cats and kittens both due to the risk of esophageal retention of a pill/capsule and due to the animal's small size. The commercially available oral liquid is not concentrated enough to keep the number of milliliters of liquid as small as possible in order to use it to compound a preparation to appropriately dose these small animals. The commercially available formulations are also not available in a flavor that will allow for effective treatment of animals with teeth and claws (they are so bitter, in fact, that kittens will froth at the mouth and vomit).

Likewise, FDA will not allow the use of Gabapentin for the treatment of severe neuropathic pain in cats because, in FDA's view, there are human FDA-approved capsules and tablets that can supposedly be used to compound a suspension or oral capsule. The human FDA-approved capsules and tablets are

³ See FDA, List of Bulk Drug Substances for Compounding Office Use Drugs for Use in Nonfood-Producing Animals or Antidotes for Food-Producing Animals, <https://www.fda.gov/animal-veterinary/animal-drug-compounding/list-bulk-drug-substances-compounding-office-use-drugs-use-nonfood-producing-animals-or-antidotes> (determining that seven bulk drug substances are eligible for the List); FDA, Nominated Bulk Drug Substances That May NOT Be Used to Compound Office Use Drugs or Antidotes for Use in Animals, <https://www.fda.gov/animal-veterinary/animal-drug-compounding/nominated-bulk-drug-substances-may-not-be-used-compound-office-use-drugs-or-antidotes-use-animals> (determining that eleven bulk drug substances are not eligible for the List because there are FDA-approved drugs that can be used).

not suitable for most cats. Gabapentin available in tiny tablets is crucial for accurate dosing instead of using large capsules. The commercially available capsules and tablets are too large and breaking these capsules and/or tablets up to form a suitable compounded solution could result in inaccurate dosing and potency issues, especially in small-size cats and kittens. Nevertheless, FDA believes it knows better about how to treat these animal patients than the very veterinarians that see these patients every day.

We note, finally, that courts have routinely upheld a prescriber's right to determine the appropriate medication for treatment, by allowing prescribers to use commercially available medication off-label. *See, e.g., Travelers Indem. Co. v. Cephalon, Inc.*, 32 F. Supp. 3d 538, 544 (E.D. Pa. 2014) (“[B]ecause the FDCA does not regulate the practice of medicine, and because prescription drugs may have therapeutic uses other than their FDA-approved indications, physicians may lawfully prescribe drugs for off-label use.”); *United States v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012) (“Once FDA-approved, prescription drugs can be prescribed by doctors for both FDA-approved and -unapproved uses; the FDA generally does not regulate how physicians use approved drugs.”); *Washington Legal Found. v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000) (“A physician may prescribe a legal drug to serve any purpose that he or she deems appropriate, regardless of whether the drug has been approved for that use by the FDA.”); *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989) (“FDA approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient.”); *In re Orthopedic Bone Screw Products Liability Litigation*, MDL No. 1014, 1996 WL 107556, at *3 (E.D. Pa. Mar. 8, 1996) (“[T]he decision whether or not to use a drug for an off-label purpose is a matter of medical judgment, not of regulatory approval,” (citation and quotation marks omitted)).⁴ These off-label use cases demonstrate the court's deference to the practitioner's judgment on proper treatment—which supports allowing practitioners to choose a compounded drug over a commercially available drug where required.

In sum, GFI #256 is an unprecedented and dangerous intrusion into the State-regulated practice of veterinary medicine. It also presents serious obstacles to veterinarians which threaten their ability to properly treat their animal patients. FDA's attempt to regulate the practice of veterinary medicine is contrary to well-established legal authorities and, as a result, GFI #256 should be withdrawn.

3. GFI #256 Will Have A Profoundly Negative Impact On Animal Health

Finally, notwithstanding FDA's complete lack of authority to both issue GFI #256 and to regulate the practice of veterinary medicine, the substance of GFI #256 is deeply troubling, unworkable in its current form, and will almost certainly adversely impact animal health across the country.

As FDA is no doubt aware, the practice of veterinary medicine differs from the practice of human medicine in several ways that make access to compounded medication important for veterinarians in order to provide the course of treatment they deem most appropriate. FDA-approved medications to treat animals are not as readily available as FDA-approved medications to treat people. Moreover, unlike

⁴ *See also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350, (2001) (addressing off-label use in the context of medical devices); *Femrite v. Abbott Nw. Hosp.*, 568 N.W.2d 535, 539 n.4 (Minn. Ct. App. 1997) (addressing off-label use in the context of medical devices); *Klein v. Biscup*, 673 N.E.2d 225, 231 (Ohio Ct. App.); *Piazza v. Myers*, 33 Phila. Co. Rptr. 144, 148 (Pa. C.P. Philadelphia Co. 1997).

medical doctors, veterinarians treat a wide variety of species of animals, all of varying sizes and taste preferences, each of which face their own unique set of health conditions and disease and which require particular types, amounts, dosages, and dosage forms of medications. Finally, veterinarians' offices often serve as emergency rooms and hospitals for animal patients where time is of the essence and quality compounded drugs are often a veterinarian's first course of action for treatment.

The practice of veterinary medicine and of veterinary compounding pharmacies is, therefore, not a one-size-fits-all undertaking. Veterinarians frequently depend on pharmacies to compound medications that meet the particular needs of their animal patients, often to a greater degree than medical doctors and in ways that are unique to the nature of the practice of veterinary medicine. In many instances, even if there is an FDA-approved product available, that product is not appropriate for all of the wide variety of different types of animals treated by veterinarians. For example, providing a medication for a cat in a flavored liquid form instead of in pill form often leads to increased compliance because it is easier for the cat's owner to administer a liquid than to get the cat to swallow a pill. Increased compliance means the animals are actually getting the medication they need.

As a result, unnecessary and ill-conceived restrictions on veterinarians' ability to appropriately treat their animal patients will cause patient harm. GFI #256 must be withdrawn because (1) it supports, without justification, starting compounding with FDA-approved drugs rather than bulk active pharmaceutical ingredients, which is known to decrease quality and increase risk, unnecessary and even dangerous ingredients, and cost; (2) it will essentially eliminate the ability to use bulk substances to prepare compounded animal medication for office use which will put animal health at risk; and (3) it will drastically increase the costs of critical compounded medication to such an extent that animal patients will be forced to go without medical care.

(a) Supporting the Use of FDA-Approved Drugs Over Bulk Substances for Compounding Puts Animal Health At Risk.

First, it is plainly apparent that FDA would, in all circumstances, prefer veterinary compounders to use FDA-approved human or animal drugs as the source of their API over that of bulk substances.⁵ FDA supports this approach on the basis that FDA-approved drugs are supposedly safer than bulk substances due mainly to three reasons:

- FDA approved drugs go through the new drug approval process where they are reviewed and approved by FDA for safety and efficacy;
- FDA approved drugs are produced under cGMP standards; and
- FDA approved drugs must have adequate directions for use, which includes information such as indications, dosing, side effects, and drug interactions.

⁵ FDA has, for example already chosen to exclude *eleven* bulk substances from the List on the basis that the preparation to be compounded can be made using an FDA-approved human or animal drug. See FDA, Nominated Bulk Drug Substances That May NOT Be Used To Compound Office Use Drugs or Antidotes for Use in Animals, <https://www.fda.gov/animal-veterinary/animal-drug-compounding/nominated-bulk-drug-substances-may-not-be-used-compound-office-use-drugs-or-antidotes-use-animals>.

FDA offers no scientific reason or rationale for this approach and, in fact, there are many instances in which using FDA-approved drugs to compound medication is risky. As a threshold matter, it should never be assumed that human FDA-approved drugs are safer for animals than bulk substances. Animals are not small humans. Commercially available drugs specifically approved for human use are often made in particular dosage forms, in routes of administration, and with ingredients that are not applicable to many animals (small animals, exotic animals, baby animals, etc.). For example, commercial drugs intended for humans often have flavorings such as Xylitol that are dangerous to pets. In such cases, even if there is an appropriate commercial strength for a pet, it cannot be used due to the Xylitol. In such cases, compounding is the only choice and it must be compounded from a bulk source that does not contain Xylitol or other products dangerous to animals.

In addition, in supporting the use of FDA-approved drugs, FDA ignores the unique nature of the new drug approval process compared to compounding. For example, FDA approves safety and efficacy for finished drug products based on information that is specific to an API, in a specific strength, within a specific dosage form, and given by a specific route of administration. Using an FDA-approved drug as the starting ingredient in a compound will likely alter all of these factors. There is, therefore, no scientific basis to conclude compounds produced from FDA-approved drugs will have any of the same safety and efficacy characteristics as the FDA-approved drug itself.

Likewise, individual dosage units of FDA-approved medications can vary from their purported strength by as much as +/- 15%. Starting with API that could be +/- 15% off from what the compounder is expecting could lead to finished compounded preparations that are sub-potent or super-potent when compared to finished compounded preparations that utilized a bulk API with a known level of potency. As a result, the commercially available formulation cannot always be used and compound preparations must often be made from bulk ingredients. Even when utilizing a human health FDA-approved medication in preparing a very simple compound, such as diluting a higher strength solution to achieve a dose appropriate for an animal, the compounder may be inadvertently incorporating excipients into that compound that are toxic for that animal patient. In contrast, bulk ingredients are obtained from FDA-registered suppliers and each batch comes with certificates of authority that document potency. Starting with bulk ingredients allows compounders to achieve a higher level of accuracy with regard to potency.

Finally, we note that many drug manufacturers will not (or cannot) permit sales of finished goods to compounding pharmacies, thus preventing compounding from FDA-approved sources. For example, Lomustine is prescribed to treat several types of cancer in dogs and cats. The only commercially available form of this medication is Gleostine in 10mg, 40mg, and 100mg strengths. The manufacturer of Gleostine prohibits the sale of it to compounding pharmacies. Another example is Isotretinoin. Isotretinoin is used to treat a variety of oftentimes serious dermatologic conditions in dogs. Isotretinoin is commercially available in capsule form in 8mg, 10mg, 20mg, 30mg, 32mg, 35mg, and 40mg strengths. Due to its teratogenic effects, both the patient and physician must register with the REMS program iPledge in order to prescribe Isotretinoin. Veterinarians and veterinary patients cannot register in the iPledge program, and the medication cannot be acquired by a compounding pharmacy despite its commercial availability. Thus, even if a product could be compounded using FDA-approved ingredients, there is no certainty that such ingredients will be available to compounders. Inevitably, this will disrupt patient treatment and prevent animals from obtaining the medication they need – medication that could just as easily and safely be made using bulk ingredients. There is, therefore, no justification for why compounding using an FDA-approved

drug product is in any way superior to using a bulk drug substance and no justification for the restrictions proposed for the use of bulk substances. That FDA blindly insists on using FDA-approved drugs for API puts animal health at risk.

(b) GFI #256 Will Effectively Eliminate The Ability to Use Bulk Substances to Prepare Compounded Animal Medication for Office Use.

In addition, FDA's decision to create the List in order for veterinarians to prescribe compounded medication using bulk drug substances for office use will, in no uncertain terms, effectively eliminate office use for veterinary medication.

We must stress, at the outset, that the accessibility of office use compounded medications is *essential* for the treatment of a wide-variety of circumstances involving animal health and, therefore, any limitations on office use should be cautiously considered. 94% of veterinarians report that maintaining office use of compounded medications is important or very important to medical outcomes. Unlike human medical doctors, veterinarians' offices often serve as emergency rooms, hospitals, and pharmacies for animal patients. Veterinarians must, in many instances, travel to their animal patients for on-site treatment. For example, veterinarians treating horses at a barn or animals in a zoo must do so on-site as such animals cannot travel to a veterinary office for treatment. As a result, the unique nature of veterinary medicine frequently requires *immediate* access to compounded medications for office use, *i.e.* compounded medication that is readily available, in the veterinarian's office or to travel with the veterinarian, to treat animal patients in emergent situations or off-site. Without access to compounded medications for office use animal patients would not receive the medical treatment they often desperately need. To give a couple of examples:

- **Griseofulvin** is an anti-fungal that treats ringworm in both large and small animals. Ringworm is a fungal infection that is zoonotic, that is, it can be transferred from animals to humans. Veterinarians need compounded Griseofulvin on hand, in their offices, to immediately treat animals who present with ringworm to prevent an outbreak. Although there are commercial forms of Griseofulvin, the commercially available product is not appropriate for treating all types of animals. Ringworm causes a painful, itchy, scaly circular mark below the skin and hair loss on the scalp. It is highly contagious and can spread quickly among humans—it can be transmitted from human to human, object to human, or animal to human. Veterinarians need compounded Griseofulvin in their offices to immediately treat their animal patient and apprehend any potential ringworm outbreak.
- **Ticarcillin/clavulanic acid** is an antibiotic used to ensure that mares are free of infection before breeding. Just prior to breeding, a mare would be checked for readiness to be bred and, if ready, the mare would be flushed and bred within hours. If the mare is not bred within hours, the chances of getting a foal this cycle is not likely. This compound is not commercially available. Moreover, there is no time to order a patient specific compound when the compound is deemed necessary for

the treatment of a mare. 29,218 thoroughbred mares were bred in North America last year and ticarcillin/clavulanic acid is best practice.

- **Antibiotic/Antiviral/Antifungal ophthalmic preparations** must be available on hand in the veterinarians' offices to administer immediately to animal patients prevent further damage to the eye (or even possible blindness) following injury or infection. In addition, veterinary staff often needs to demonstrate to the pet parent how to administer the medication and then will need to send home the "demonstration" medication with the patient to prevent contamination (the tube or bottle cannot be used on another animal patient). Some examples of such preparations include:
 - Chloramphenicol is used to treat surface ocular infections involving the conjunctiva and/or cornea caused by chloramphenicol-susceptible organisms. Chloramphenicol is a broad-spectrum antibiotic agent, with generally good activity against gram-positive, gram-negative, and intracellular organisms. It is not commercially available.
 - Oxytetracycline is used to treated superficial ocular infections involving the conjunctiva and/or cornea caused by the oxytetracycline organisms.
 - Cidofovir is indicated for topical treatment of feline herpesvirus keratitis. When compared to other ophthalmic antiviral agents – shorter treatment duration & less frequent administration is required. There are no commercially available alternatives available.
 - Idoxuridine is a topical treatment of feline herpesvirus conjunctivitis & keratitis. It is not commercially available.
 - Itraconazole/DMSO is primarily used to treat fungal keratitis in horses.
 - Miconazole is used to treat ocular surface fungal infections. It is not commercially available as an ophthalmic preparation.
 - Voriconazole is used to treat fungal keratitis most commonly in horses but also in other species. It is not commercially available as an ophthalmic preparation.

Without compounded medication like the above available for office use, veterinarians would not be able to appropriately and adequately treat their animal patients.

The criteria FDA suggests for inclusion on the List will unnecessarily restrict veterinarians' access to important compounded medications for office use. For example, FDA recommends limiting the List to bulk ingredients which will be used to compound drugs only where "immediate treatment with the compounded drug is necessary to avoid animal suffering or death." GFI #256 at Appendix. There is no

statutory or other authority for FDA to prohibit compounding from bulk ingredients in all situations other than those where “immediate treatment” is necessary. A positive list with this type of onerous restriction will adversely affect animal health by making important compounded drugs unavailable.

As it stands, FDA has so far only included seven bulk ingredients on the List and only for use in certain medication regimens for dogs, cats and horses. Veterinarians use over 450 active pharmaceutical ingredients to meet the wide-variety of needs of their animal patients. Unfortunately, the evaluation criteria that FDA intends to use to determine whether a bulk drug substance should be included on the List sets the bar so high that it is likely that no other substances will make it onto the List. First, the information requested on page 16 of the GFI #256 is akin to information that would be elicited for purposes of a detailed scientific study. Among other things, FDA requests:

1. A **bibliography of scientific literature** containing safety and effectiveness data for the drug compounded using the nominated bulk drug substance;
2. An **explanation, supported by relevant scientific literature or other evidence**, of why a compounded drug is necessary;
3. **Confirmation, using supporting evidence**, that there are no marketed FDA-approved animal or human drugs that could be prescribed in an extralabel manner to treat the condition(s) in the species that the drug compounded with the nominated bulk drug substance is intended to address;
4. If the nominated bulk drug substance is an active ingredient in a marketed FDA-approved animal or human drug, **an explanation, supported by appropriate scientific data or information**, of why the animal drug cannot be compounded from the marketed FDA-approved animal or human drug under 21 CFR 530.13(b);
5. **An explanation, supported by relevant scientific literature or other evidence**, of why the animal drug to be compounded with the nominated bulk drug substance must be available to the veterinarian for immediate treatment to avoid animal suffering or death. Nominations should include **specific information documenting that animal suffering or death will result** if treatment is delayed until a compounded animal drug can be obtained pursuant to a prescription for an individually identified animal; and
6. A description of any human user or animal safety concerns associated with use of the nominated bulk drug substance or finished compounded drug for the condition(s) in the species that the compounded drug is intended to address. If there are concerns, an **explanation, supported by scientific literature or other evidence**, of why the concerns should not preclude inclusion of that nominated bulk drug substance on the List.

See GFI #256 at p. 16 (emphasis added). The information sought is nothing short of a scientific treatise, and the burden to provide this level of detail has been placed squarely on the shoulders of the animal health industry. Veterinarians and pharmacists will need to spend countless man hours, use teams of people, and marshal untold resources and money to deliver the level of scientific study necessary to “prove” the need for a bulk drug substance. It is important to note that many ingredients that are used to treat rare or semi-rare conditions are critical for the animal patients, but will not be nominated because of the lack of economic incentive to invest the resources necessary to nominate such drugs to the List. Over

100 substances have already been nominated for the List and all of them have been deemed by FDA as having been nominated without sufficient evidence.⁶ How can industry stakeholders possibly meet this burden and still maintain established standards of care?

What FDA asks of the veterinary compounding industry is, in essence, to undertake a “mini” new drug approval process for each bulk substance it needs to use for compounding animal medication for office use. This is completely unworkable for compounded drugs. By approving the use of a bulk substance only if FDA decides that there are no commercially available alternatives that can treat a condition, FDA overlooks why compounding is necessary in the first place, *i.e.*, there are too many animal species, sizes, and conditions to treat with just commercially available drugs and, as a result, compounded medication using bulk substances is vitally necessary to treat a wide-variety of animal patients. Today, compounding pharmacies specializing in animal health compound at least 40,000 different formulations using over 450 active pharmaceutical ingredients to serve the wide-variety of animal species treated throughout the country. The “mini” new drug approval process proposed in GFI #256, however, fails to recognize this and, instead, is expressly geared towards one-size-fits all products and requires the kind of information and data that can only be obtained from commercial drug manufacturers. FDA’s rigid and extensive list of information needed to evaluate the necessity of a bulk substance misses why compounding is necessary in the first place – to ensure that there is enough flexibility to treat the entire animal population. With a positive list designed purely to limit compounding from bulk substances, veterinarians will lose the flexibility that compounding provides, because commercially available drugs are, in many cases, inadequate or contraindicated for treatment.

Moreover, the bulks that FDA has approved on its proposed positive list are approved by indication, specific dosage form, and route of administration—just like new drug approval, which approves a finished drug product in a specific dosage form and route of administration to treat a specific condition. Similarly, the bulks listed on the proposed negative list prohibits bulks by indication, dosage form, and route of administration—meaning, FDA is prohibiting compounding with certain bulks in certain dosage forms and routes of administration to treat specific conditions. This is utterly inappropriate for compounds—which are universally recognized as a bad fit for the new drug approval process, as they are used to treat a variety of indications, patient populations, and species.⁷ FDA is extrapolating based on one indication, one dosage form, and one route of administration, that certain bulks will never be appropriate for any drug compounded for office use. There is no scientific justification to eliminate compounded medication for office use in this manner, and it will lead to entire animal populations going untreated.

⁶ See FDA, Bulk Drug Substances Nominated Without Sufficient Supporting Evidence, <https://www.fda.gov/animal-veterinary/animal-drug-compounding/bulk-drug-substances-nominated-without-sufficient-supporting-evidence>.

⁷ In particular, we note that asking for nominations based on “indication” is outside of the scope of compounding pharmacy. The burden of understanding the use of a medication is on the practitioner. Drug manufacturers develop drugs for indications. Compounding pharmacies, on the other hand, respond to prescriptions from practitioners that prescribe a specific formulation to meet a unique need of an animal patient. Compounding pharmacies play no role in determining an “indication” for a compounded medication, *i.e.*, pharmacies do not seek out disease states to develop drug formulations. They receive prescriptions from medical professionals and fill them. Yet, per GFI #256, FDA appears to require compounders to do a mini new drug approval, as if they were drug manufacturers. This is completely counterintuitive and reflects a complete failure to understand the nature of compounding pharmacies.

Lastly, FDA has not set forth any guardrails or guidance for how it intends to appropriately evaluate these criteria and how long this process will take. FDA is certainly not qualified to undertake the analysis and, frankly, without an independent panel of experts that are skilled in the practice of veterinary medicine, the practice of pharmacy and the nature of compounded animal medication, any decisions made by FDA will be immediately suspect and questioned. Likewise, given the level of detail requested by FDA, evaluating the submitted criteria will take months, if not years. In the meantime, veterinarians will have no way to use the nominated bulk drug substances for patient treatment and animals will suffer.⁸

FDA has, in essence, set a complete bar to getting any other bulk drug substances onto the List. With only seven bulk substances from which to choose from in order to compound medication for office use, FDA has hamstrung veterinarians and compounders and eliminated the ability to prescribe office use medication necessary to treat animal patients.

(c) GFI #256 Will Needlessly Increase The Cost Of Critical Compounded Medication, Resulting In Reduced Access to Treatment and, Ultimately, Patient Harm.

Finally, we wish to note that GFI #256 will significantly increase treatment costs and could lead to animal injury, lower quality of life, and, potentially, death. Limiting the ability of veterinarians to prescribe, and pharmacies to compound, medication using bulk substances will needlessly increase the cost of compounded medication across the board. As a result, the GFI #256 will force pet parents (who more often than not consider their pets to be family members) as well as other industry stakeholders like animal shelters and zoos, to make difficult and heartbreaking decisions about whether to forgo treatment for animal patients.

First, it costs, on average, 300% more for compounding pharmacies to purchase FDA-approved products over raw materials in order to compound medication. One compounding pharmacy conducted an analysis of more than eight of the most-frequently prescribed compounded medications for pets made from bulk APIs, which represent about 45% of all prescriptions filled by the pharmacy. The results revealed that, if that pharmacy were required to make those prescriptions from finished pills, tablets, capsules, or vials of liquid, the cost for the compounded medication would increase between 50% and 3,000%, with the average being around 300%. The increased cost is primarily the result of two factors: (1) FDA-approved products are significantly more expensive than raw materials; and (2) the effort required to compound from finished products as opposed to raw materials necessarily increases the cost of the finished product. Compounding pharmacies will need to pay significantly more to obtain finished products if they intend to compound medication. For example, it would cost a pet owner approximately \$600/month to treat their dog diagnosed with Addison's Disease, or hypoadrenocorticism, with FDA-approved Florinef tablets (10 tablets twice daily). Alternatively, the veterinarian could prescribe

⁸ We note that, per GFI #256, FDA will only include bulk drug substances on the List if, among other things, "immediate treatment with the compounded drug is necessary to avoid animal suffering and death." How does FDA reconcile the lengthy and time consuming nature of what will certainly be the evaluation process to determine whether a bulk substance will be included on the List with the fact that the primary basis for their nomination is that the substance is needed to treat patients in emergency circumstances? How can veterinarians effectively treat their patients while they wait for confirmation that the bulk substance has made it onto the List?

compounded Fludrocortisone capsules at \$66 for 100 tablets. As a result, the cost of compounded medication will, on the whole, increase dramatically as a result of GFI #256.

The increased cost will inevitably lead to a decrease in treatment, a reduced quality of life for the animal, and the potential death of animal patients. It is critical to understand that the animal health industry is *fundamentally different* from the human health industry. For one thing, the unfortunate reality is that when faced with whether to pay for healthcare for a human family member or a family pet, the family pet must come second. In addition, most pet parents do not have insurance for their pets. When offered, moreover, animal insurance can be costly and vary wildly in terms of coverage with many insurance companies not offering any pharmacy benefits. As a result, the vast majority of pet parents in the U.S. pay out of pocket for all their animal's health needs. Even a small increase in the cost of medication will, as a result, lead to a decrease in treatment compliance (as pet parents will choose not to pay for an entire course of medication treatment), will reduce the animal's quality of life without medication, and, even worse, will lead to early euthanasia for animal patients that have treatable or short-term conditions because pet parents simply cannot afford the medication and/or treatment. For example, elderly individuals on fixed incomes will be forced to make hard choices with regard to their pets' wellbeing if their pet's medication costs increased. To be blunt, the cost of compounded animal medication will be the difference between life and death for many animal patients, and will inevitably be the cause of severe stress for the pet owner. This cannot be the intention of an agency that focuses on the health and wellbeing of humans and animals alike.

Pet parents are not the only ones who will be forced to make hard decisions if the cost of compounded medication goes up. Animal shelters and low-income animal rescue clinics, for example, often rely on compounded medications to keep their low cost clinics running. At an animal shelter, veterinarians cannot guarantee what kind of animal will come through their doors in need of care, and, accordingly, veterinarians need to have multiple formulations and drug combinations available to treat a variety of animals of all different ages, weights, sizes, and temperaments. And, it is critical that veterinarians at shelters have access to formulations that are palatable to different animals to decrease the time it takes to safely medicate a wide variety, and large number, of animals with different temperaments. Relegating animal shelter veterinarians to medications compounded from FDA-approved products forces these critical medications so far outside a shelter's budget that the animal shelter residents will be deprived of the medical care they need and deserve.

Likewise, zoos are also put in the precarious position of needing to treat exotic animals of all shapes, sizes, and temperaments. The availability of compounded drugs from bulk allows zoo veterinarians to treat these animals in a cost effective manner. For example, three Asian Elephants residing at the Oregon Zoo in Portland, Oregon were diagnosed with multi-drug resistant tuberculosis. The veterinarian prescribed the standard treatment protocol that consisted of five drugs given orally or rectally once daily for a minimum of 9 months (i.e., 270 days). The drugs were Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA), Ethambutol (EMB), and Enrofloxacin (ENR). The average Asian Elephant weighs 12,000 pounds, and the daily dose of each drug was INH 28 grams, RIF 49 grams, PZA 164 grams, EMB 164 grams and ENR 14 grams. By compounding these drugs from bulk ingredients, treatment for ***all three elephants*** was able to be provided for \$279/day. However, if relegated to only FDA-approved animal or human drugs, treatment for all three elephants would have cost \$6,261/day. Using FDA-approved drugs, the total 9-month course of therapy for these elephants would have cost over \$1.5 million—an amount

well beyond the ability of a standard zoo to pay. If FDA-approved medications were the only option, all three elephants likely would have been euthanized. Instead, this 9-month course of therapy for the three Asian Elephants cost \$75,000. These elephants are alive and well today—thanks to the availability of compounded medication made from bulk ingredients.

In conclusion, GFI #256 will significantly increase treatment costs for animal patients, which is likely to lead to placing the animal's medical care far outside the budgets of pet parents, animal shelters, and zoos. Without the means to pay for the average 300% markup on compounded medications under GFI #256, these animal patients will go without care. Even worse, euthanasia will increasingly become the more cost-effective option. These needless restrictions on veterinarians' ability to treat their animal patients will cause significant patient harm, and GFI #256 must be withdrawn.

4. Conclusion

The veterinary compounding industry has a well-regulated system of state laws that already works to serve the needs of animals and veterinarians. There is no authority for the GFI #256 and no justification for the substance of the guidance set forth therein. Accordingly, we respectfully request that FDA withdraw GFI #256 and request that CVM strongly consider engaging in further dialogue with members of this coalition, as well as other industry stakeholders, on the best path forward to appropriately regulate veterinary compounding. To that end, we respectfully request a formal meeting with CVM leadership to discuss our concerns with GFI #256 in greater detail.

Regards,

Rachael G. Pontikes

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