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PHARMACY

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October 14, 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:

Wedgewood Village Pharmacy ("Wedgewood" or "Wedgewood Pharmacy") is a pharmacy specializing in compounding medication for animal patients. Wedgewood serves tens of thousands of veterinarians and 350,000 patients annually throughout the United States and has provided compounded drugs to patients for more than forty years. As licensed professionals specializing in animal health, we have a deep understanding of and are deeply committed to the safety and care of our patients. Because of the breadth and depth of our experience, we believe we are uniquely situated to articulate practical comments to FDA's draft Guidance for Industry #256: Compounding Animal Drugs from Bulk Drug Substances ("GFI #256" or this "Guidance"). It is with this great responsibility and the health and safety of the animals that contribute so deeply to the human experience that we offer these comments to FDA on GFI #256.

We note as a preliminary matter that, except as we outline in Section VI.(e) below, none of our comments apply to the use of compounded medications in food producing animals. We believe that the uncertainty and potential risks presented by the lack of Food and Drug Administration ("FDA") oversight of medications used in animals that are part of the food chain food greatly outweigh benefits unless these risks are studied. Accordingly, we are supportive of efforts FDA makes to limit use of compounded drugs in animals that are part of the food chain. In fact, we feel FDA should consider limiting any final guidance regarding animal health compounding from bulk ingredients to guidance for its use in food-producing animals.

We also note as a preliminary matter that we strongly believe that the FDA does not have the legal authority to regulate veterinary compounding. We are aware of and have participated in comments

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to FDA over the years in support of these legal arguments. Without belaboring these legal points as set forth in our prior submissions, we incorporate them by reference and would be happy to forward them separately if you should want to re-review specifics. In brief, these matters are properly and lawfully reserved for states to address, including through their respective board of pharmacies. It is state boards of pharmacy, not FDA, that can best consider these issues and address them consistent with the realities of veterinary and pharmacy practice—and with the needs of animal patients and their owners—within their borders. We remain hopeful that if FDA finalizes animal health compounding guidance, it will be responsive to comments presented by Wedgewood, other compounding pharmacies, and practicing veterinarians in a variety of specialties, who understand the risks and benefits of animal health compounding from bulk drug substances the best.

We also urge FDA to take an approach that is driven by science, medicine, empirics and the actual experience of veterinarians and pharmacists who deal every day in their practices with these issues, all of which are conspicuously absent from FDA's proposal for GFI #256. Most fundamentally, FDA has not established a substantive predicate for revising its approach to animal health compounding. At a time when federal regulation is, if anything, excessive, and when the Administration has committed to roll back excessive regulation, FDA should not be proposing a dangerous expansion without first establishing a need for it. As we explain, however, FDA is now proposing drastic, unsettling change in the relevant framework to address supposed problems that seem more imagined than real—and that FDA has not even shown to exist, let alone attempted to study, in any rigorous or serious way. Before FDA overhauls established medical and pharmacy practice in this fashion, it should establish adequate warrant to do so. Because such warrant is lacking here and because there are clear indications that GFI #256 would do more harm than good, we believe GFI #256 would be vulnerable to legal challenge should such a challenge prove necessary.

I. Issues in draft GFI #256 that Raise Little Concern

Although we differ from FDA on the matter of legal authority, we are conceptually aligned with the thinking behind portions of these seven provisions, with exceptions as noted:

(a) **Limited use in food-producing animals**. As noted above and in Section VI.(e) below, Wedgewood is in favor of regulations restricting the use of compounded medications in food producing animals to very limited cases and defers to specialists in production animal medicine for specific recommendations.

(b) **Requirement for a veterinarian client patient relationship ("VCPR")**. Several of the provisions of GFI #256 suggest that a VCPR exist. We support FDA's thinking that the decision to prescribe or dispense a compounded medication for a patient or group of patients with similar unique needs rests with the prescribing veterinarian, who should have a relationship with the patient and the caregiver.

(c) **Prohibition of compounding drugs that are exact copies of commercially available products**. Clearly a veterinarian has, using their medical judgement, the authority to decide if an FDA-approved drug meets the needs of their patient. If an FDA-approved drug is appropriate, we agree with FDA's opinion that a veterinarian should prescribe, administer or dispense that FDA-approved

medication. If the prescriber feels that the unique needs of their patient cannot be met by an FDA-approved drug, the authority to order or prescribe a compounded medication should be available without the need to document medical rationale outside of their usual course. Additionally, pharmacists should maintain standard operating procedures and enact controls to ensure that they are not compounding exact copies of FDA-approved medication that are available through normal distribution channels. While we believe exact copies are not appropriate, as noted below, we strongly disagree with the expansive definition of what constitutes a copy in GFI #256 and we strongly disagree that FDA has authority to practice veterinary medicine by telling veterinarians what they can and cannot prescribe. If anything, FDA's could suggest that a pharmacy be able to demonstrate via an SOP how they ensure that they do not prepare exact copies of commercially available medication.

(d) **Supervision**. We agree with FDA's opinion, and most state regulation, that compounding must be performed under the direct supervision of a veterinarian or pharmacist.

(e) **Requirement for adverse event reporting**. We believe a process for capturing, investigating and taking corrective action on adverse events and complaints is imperative for compounding pharmacists. Many if not most states require reporting of serious adverse events and recalls. While we agree that adverse event reporting is important, the first notification requirement should be to the pharmacy—not the FDA—so that the pharmacy may initiate an immediate investigation and corrective action, if appropriate, to reduce potential patient impact. The second notification should be to the state board of pharmacy, who can respond more quickly than a federal agency. There is a possible opportunity to collaborate with veterinarians and pharmacists to develop, align and strengthen a state-based adverse event reporting system and we welcome the opportunity to actively participate in this collaboration. We note, however, that (i) FDA as the first line of reporting when the response is typically delayed risks patient health, and (ii) any adverse event reporting should be limited to series adverse events, as defined in state law.

(f) **Office Use**. We agree that veterinarians need to order medications for office use and office stock. Office use is not just appropriate but critical for veterinarians, as they act as hospitals, emergency rooms, surgical centers, etc. Can you imagine going to a human health hospital and they don't have the needed medication on hand? We strongly disagree with FDA's approach to limit office use. As there are many different specialties, office use should remain the jurisdiction of the states, along with the veterinarian who determine what medication they must keep on hand to treat their unique patients. Today most state regulations permit office use.

(g) **Veterinarian Dispensing.** We agree that veterinarians should be permitted to dispense medication to their patients, as long as a VCPR exists. Especially for medication outside of flea and tick and heartworm category, along with some human health generics used in animal health, community pharmacies do not generally stock medication needed for animal patients, unless they are compounding pharmacies. There are not compounding pharmacies in every community, and those that are local generally have limited hours. Therefore, it is imperative that when treatment needs to begin immediately, and even for caregiver

convenience and compliance, veterinarians need to be able to have medication on hand for dispensing.

II. Compounding from bulk active pharmaceutical ingredients secured from FDA-registered and inspected suppliers of chemicals is safer and more reliable than compounding from FDA approved finished product and prevents unnecessary and significant cost increases that are punitive for patients with special needs and their caregivers.

(a) Permitting compounding from bulk in human health and not animal health is illogical

(i) Federal regulations and guidance in human health explicitly permit compounding from bulk active pharmaceutical ingredients. The manufacturing and repackaging of bulk active pharmaceutical ingredients are explicitly regulated by FDA. There has never been a suggestion from CDER or state regulatory authorities that compounding from finished goods is safer in human health, and it makes no sense that it would be safer for animal patients. Specially requiring veterinarians and pharmacists to compound from FDA approved finished goods instead of bulk ingredients solely within the veterinary realm may further the profits and interests of drug manufacturer (which focus upon human rather than animal patients) but it otherwise makes no sense from a regulatory or medical perspective. In addition to the burdensome administrative hurdles put forth by FDA in this Guidance, trying to prevent access to medications compounded from bulk ingredients increases cost, lowers quality, and corrodes the trust of the practicing veterinarian. It suffices to note that compounding from bulk has not been shown to pose any greater risks to animal patients as compared to human patients, and FDA should not regulate on a contrary premise, as GFI #256 would. Veterinarians and pharmacists should not be forced, under the guise of safety, to disserve the interests of animal patients in ways that FDA has not seen fit to do with human patients.

(b) Claims that Drugs Compounded With FDA-Approved Finished Goods are Safer is Unfounded

(i) In the "Policy" Section of GFI #256, FDA proposes that guidance is meant to address FDA's "current understanding of the risks of compounding animal drugs from bulk drug substances." While these risks are generally described to include; "superpotency leading to animal overdose, microbial contamination, and drug formulations that present safety risks for the treated animal or for people handling or administering the animal drug," FDA gives no examples or scientific evidence that document risks related specifically to the use of bulk ingredients. The guidance does not provide a basis for FDA's assertion that a product made from a bulk drug presents any more risk than a finished drug product made from the same active

pharmaceutical ingredient ("API"). There is no evidence, scientific or otherwise, that FDA or any other party has studied these matters in any way; certainly, FDA has not pointed to any such evidence or science, which could in turn spark informed comment and deliberation. The vast majority of drugs that animal health compounding pharmacies regularly produce from bulk ingredients are old, off-patent drugs that are standards of practice in veterinary medicine. Veterinarians have vast clinical experience using these medications in their practices for those patients whose unique needs cannot be met by manufactured drugs, and are suspect, based on their clinical observations for many years, to FDA's claims that they have in some way missed common dangers. We believe and are confident that veterinarians and pharmacists working together to solve unique clinical challenges is an appropriate framework. We would be happy to work with veterinary schools, as we have done in the past, to supply medication to further the knowledge of compounded medication and its clinical use.

(ii) Of the millions of compounded drugs that have been prescribed for animal health, FDA has pointed in presentations it has given on this matter (but not in the actual proposal for GFI #256) to three separate incidents where a total of 28 animals died. These examples are: (A) an incident in 2009 where 21 horses died when compounded vitamin and mineral injection solutions were made with 100x amount of selenium, (B) an incident in 2014 where 4 horses died when a toltrazuril/pyrimethamine oral suspension was made with 20x the amount of pyrimethamine and (C) an incident in 2019 where 3 horses died when a toltrazuril/pyrimethamine oral paste contained 18-21x the amount of pyrimethamine. While these events were certainly tragic, we strongly believe that the root cause of each event was human error that could have occurred regardless of whether the compounder was starting with an FDA approved product or a bulk drug ingredient. As tragic as these events were, the scheme proposed by GFI # 256 would have done nothing to prevent these tragedies because they have nothing to do with compounding from bulk ingredients. We believe that pointing to incidents whose root causes are unrelated to the actual proposal causes mass confusion on the issue and does not advance the cause of safety of drugs.

(iii) Microbial contamination can occur any time a drug substance is introduced to an aqueous environment. This is even more likely if there are substrates present that support microbial growth, such as bulking agents like lactose, used in the formulation of many FDA-approved finished drugs. Hazardous drug substances make up a large proportion of compounded animal drugs and are frequently dispensed in a specific strength and dosage-form that enhances patient acceptance and reduces the risk of exposure for the person administering the drug. This provides a much safer experience for both patient and pet-owner than splitting or cutting tablets or opening capsules, where the contents may become airborne and inhaled.

(iv) Beginning with finished drug products requires crushing, grinding, manipulation or other additional processes that would not be required if bulk ingredients were used as the pharmacist must handle many vials and

ampules to compound a batch of a sterile preparation and crush or open many tablets or capsules. Each such additional process creates additional opportunity for human error and thus adds unnecessary risk to the production process.

(c) Difficulty in Ensuring Potency

(i) The amount of API contained in a drug is a critical factor in determining both whether a drug will be effective to treat a disease or condition and whether that drug could have harmful effects. We are deeply concerned that if we are required to begin compounding with finished goods our ability to produce drugs with consistent potency will be severely compromised.

(ii) Finished pharmaceutical products are allowed a considerable amount of variance in the actual amount of active ingredient contained therein. Typically, the relevant guidelines allow an average variance of ±10% of the stated dosage on the label. This variance, however, is averaged over multiple doses (e.g., all tablets in a bottle) to achieve the labeled potency. But for individual dosage units—like a single pill—the allowed variance may be 15%. The allowable potency variance for compounds is +/- 10%, however testing of most preparations compounded from bulk API typically shows potency that is within 5% of the labeled strength. This can only be achieved by knowing the exact amount and potency of the bulk active ingredient being used as the starting component. In contrast a compounded prescription made from a single dosage unit (e.g., from crushing a pill), having a potential variation in the active ingredient of 15% would mean that the compounded preparation could have a variation of up to ±25%. A finished compounded preparation with an active ingredient strength that is ±25% of the strength that was prescribed could result in a subpotent or superpotent dosage, either of which could have a significant impact on a patient's health.

(d) Unneeded and Potentially Dangerous Excipients

(i) When a drug is compounded to meet the identified needs of a patient, it is the best practice to use only the ingredients necessary to produce the prescribed medication in the applicable dosage form. This means starting with API in its purest form, and then adding only the ingredients necessary to achieve the prescribed dosage-form, strength and flavor. Bulk drug substances are APIs in their purest, verified form, accompanied by a certificate of analysis as required by the United States Pharmacopeia and federal law. Using USP-grade bulk ingredients from FDA-registered and inspected suppliers is the surest, safest, and most scientific way to meet the unique needs of a patient.

(ii) Finished drugs contain many ingredients other than API. These other ingredients, or excipients, may be fillers, binders, dyes, flavorings, preservatives or other materials. These are added to a formulation for

specific reasons related to the actual drug and dosage form being produced. These excipients typically cannot be separated from the API and the excipients and the amounts contained in any particular finished drug product may not be known. A particular excipient that may be common and serve a particular purpose in one dosage form may not be appropriate to use in another dosage form. Thus, if required to compound from finished drug products pharmacies and veterinarians would be required to produce a product that contains components and amounts of such components they could not specifically identify or measure. In addition to mandating a poor compounding process, excipients that could cause harm or variations in potency may create significant product liability which could discourage the production of needed drugs.

(iii) Compliance with dosage regimens is a significant barrier to properly treating many conditions in animals. Because excipients alter the texture, taste and palatability of a drug, the inclusion of unknown excipients greatly increase the difficulty in dosing animals.

(iv) Because a compounded drug made from a finished product contains unknown excipients, these drugs present significant risk to patients. Many FDA-approved finished products (and particularly those made for human use) contain excipients that can be toxic to different animal populations. For example, the sweetener Xylitol is toxic to dogs and the preservative Benzyl Alcohol is toxic to cats.

(v) Unneeded excipients can add significant volume to a finished product making it quite difficult to make small dosage sizes that are critical to smaller patients like cats, rabbits or birds. Additionally, commercial products that are only available in small dosage sizes may make it very difficult to produce large dosage sizes that are necessary when treating elephants, whales and other large animals.

(e) Unavailability of Finished Products and API

(i) In many cases compounding pharmacies are unable to obtain FDA-approved animal drugs from traditional sources as the many animal drug manufacturers will not sell their products to pharmacies. Thus, the only way compounding pharmacies may be able to obtain many pharmaceutical products is to purchase the drug from a veterinarian's office. Because few veterinarian offices stock sufficient supplies of finished products to allow for compounding and because drug companies may discontinue sales to veterinarian offices if they know that these offices are selling product to compounding pharmacies, this channel creates an inadequate and unreliable source of product. In addition, the pharmacy does not know if the drug product was stored appropriately after leaving the veterinarian's office, or if it was otherwise adulterated. A pharmacist is not able to just accept a drug that a patient hands to them and compound with it.

(ii) For a variety of reasons many manufactured drugs regularly go on back order or otherwise become unavailable. These shortages can have a serious

impact on patients who are in need of drugs. In these cases, compounding pharmacies are often relied on to produce medications until supply of the manufactured drug becomes available again. If compounding pharmacies are required to compound from finished drug product (i.e. the same product that is on back order), then pharmacists would not be able to fill this critical role. Moreover, even if allowed to compound from bulk only in the situation of a drug shortage, compounding pharmacists also would not likely be able to fill this role. This is true because to respond quickly to a drug backorder, pharmacists need to have API available on hand or at least sourced when a shortage occurs. If they were only to seek out API when a shortage occurs, delivery delays or unavailability of such API are likely to make compounding to fill the patients' needs in the case of a backorder unlikely.

(f) Certain Dosage Forms Cannot Be Used to Produce Other Dosage Forms

(i) Capsules and tablets are primarily formulated to be administered as a pill swallowed whole. Because of this, there are many insoluble, unnecessary and unpalatable ingredients in these dosage forms that make it impossible or impractical to compound topical, transdermal, ophthalmic, otic, nasal, or rectal preparations from these capsules and tablets. In addition to having poor formulations, compounding from tablets will increase the amount of material to work with, subsequently increasing dose volumes, capsule sizes, and reducing or eliminating the ability to make very small tablets for small animals. For many animals, small capsules, small tablets, palatable suspensions and transdermal medications are necessary to ensure compliance with treatment regimens.

(ii) In most cases, topical preparations cannot be compounded from other dosage forms. The primary reasons for compounding topical preparations are due to either needing a higher strength than what is available, or the vehicle of the commercial product is not suitable for current application. Commercial products cannot be manipulated to produce a higher strength than what is already available. Other dosage forms such as capsules and tablets cannot be use due to inappropriate fillers that are not suitable for topical application. When treating skin conditions, oftentimes another vehicle is required due to other comorbid skin conditions, or how the drug needs to be applied. Sprays and other solutions, ointments or creams, and non-irritating dosage forms cannot be compounded with commercially manufactured drugs.

(g) Safety and Efficacy Data for Finished Drug Products Does Not Translate to Other Products

(i) FDA uses data provided by a drug manufacturer to assess the safety, efficacy, and quality of the drug being made by that manufacturer to determine whether it should be approved for use in a specified species. All

of that data, and thereby any approval FDA gave to that drug related to safety, efficacy, and quality, becomes null and void (and not applicable for approval of another drug or formulation) when that FDA approved drug is altered or manipulated in preparing a compounded medication. If such data is not relevant for approval of a different formulation, we are confused as to why compounding from finished goods, when they compounded drug will necessarily be manipulated, provides any connection to safety. For example, when FDA approves a 5mg methimazole tablet for use as a treatment for hyperthyroidism in humans, FDA is basing that approval on data that demonstrates the chemical stability of methimazole when combined with known excipients to produce a tablet, the quality and consistency of the manufacturer's process for making that tablet, and the safety and efficacy associated with the biological response of a human after swallowing a tablet. When that FDA approved 5mg methimazole tablet is crushed and mixed with liquid excipients to make a compounded oral liquid form of methimazole for a veterinary patient, all of the stability, safety, and efficacy data FDA used to approve the tablet becomes irrelevant because the only thing the compounded oral liquid has in common with the FDA approve tablet is that they both contain methimazole. FDA's rationale for the use of a finished drug product fails to acknowledge that FDA's approval of a finished medication has no relevance when that medication is transformed into a different dosage form, strength, or route of administration for use in a potentially different species.

(ii) Many of the APIs prescribed to treat animal patients are ingredients contained in drugs approved for human health. When a veterinarian uses a human health drug to treat an animal patient, they are doing so off label. No data on safety and efficacy for the use of these drugs in animal patients is available (as the studies performed to received FDA approval were done on humans), so it doesn't make sense that it would be "safer" to use a human health finished dosage form as a starting point for compounding medication for an animal patient.

(h) Conclusion

As best we can understand from GFI #256 and FDA's public and private commentary on GFI #256 the two primary reasons for this guidance are that (x) FDA's proposition that in some manner drugs compounded from bulk ingredients create more risk to animals (versus human) than compounded drugs made from finished product and (y) compounded drugs from bulk discourage drug manufacturing companies from going through the new drug approval process.

(i) We do not believe these claims are true. Dr. Loyd V. Allen Jr, a nationally renowned expert on compounding and the Editor-in-Chief of the International Journal of Pharmaceutical Compounding, wrote "The bottom line: bulk substances are the only rational source of drugs for *all* compounding activities, unless they are not available. Excipients in

commercial dosage forms also can contribute to compatibility and stability problems as well as elegance and compliance considerations."[1] We strongly agree with this statement and can see no public benefit to the premise that compounding should begin with finished product as a default position. Instead, we hope to see FDA encourage, as they already did in their thinking about adherence to USP quality standards, that compounding for animal patients begin with high-quality bulk API from FDA-registered suppliers as this is the safest, surest, most appropriate starting point.

(ii) We have never seen evidence that the drug approval process was being thwarted by compounding pharmacies in service of veterinarians and the unique needs of a small portion of animal patients that we serve. In fact, the animal health industry is doing quite well, even in the midst of a pandemic. The American Pet Products Association reports that estimated U.S. Pet Expenditures will reach $99 billion in 2020, with a 10-year compounded annual growth rate of 7.5%. A reported $11.2 billion of the 2021 estimated U.S. spend is in pet medication, with an even higher compounded annual growth rate of 8.1%. If compounding pharmacies were truly a threat to pharmaceutical manufacturers, wouldn't you see that in this data? The success of the animal health pharmaceutical industry is in its ability to enable veterinarians to treat large populations of patients that have similar needs. Compounding pharmacists are called upon when the populations of patients are small—like exotic species, pocket pets, very small patients, very large patients, and very finicky patients—or in the frequent incidences when major manufactured items go on backorder (95 times in the last 10 years). Pharmaceutical manufacturers cannot possibly serve the needs of 100% of this varied market, and FDA has admitted to clinical need for that reason. Forcing veterinarians and pharmacies to start compounding with finished goods will have the primary effect of increasing pharmaceutical manufacturer's profits from these unique and underserved patients, without manufacturers actually meeting their needs.

III. Compounding from Finished Product Will Drastically Raise the Cost of Compounded Medicine Which Will Cause Unnecessary and Unjustified Suffering

(a) We believe that a veterinarian should chose an FDA-approved drug to treat the patient when they feel that drug will meet the patient's clinical needs. We regularly communicate that a veterinarian should not request a copy of a commercial item just to "save money." However, we do NOT believe it is appropriate or fair that when the veterinarian determines that the patient's need cannot be met by an FDA-approved drug, that the veterinarian and/or caregiver should be "punished" by having to pay a higher cost (in addition to the quality concerns/risks articulated above) due to a requirement to start with finished goods. Additionally, human health drugs that are used off label in animal health in addition to generally requiring a change in dosage form and strength, are priced for insurance company

[1] Pharmacy Times, Compounding with Commercial Drugs Can Cause Errors, November 1, 2006

and Medicare reimbursement. Animal caregivers pay out of pocket, or via a non-profit entity in the case of shelters, zoos and rescues, and starting with the FDA-approved human health medication would put the cost of treatment completely out of reach, causing not just unnecessary suffering but also unnecessary euthanasia. How can FDA proport to be improving the safety for animal patients if adherence to this element of the Guidance causes actual death for untold thousands of patients of all species? Veterinarians reported in response to our survey submitted as a separate comment letter that annual deaths caused by financial-based euthanasia would far outweigh anecdotal safety incident reports from FDA.

(b) Starting with FDA-approved finished product for compounded preparations will lead to a significant increase in medication cost for the pet owner. At a time when there is great public outrage about skyrocketing prescription drug prices and with the United States in deep economic turmoil caused by the coronavirus pandemic, GFI #256 stands to cause increases of 300%-3000% for animal drugs. While FDA often maintains that cost should not be a factor when determining therapeutic options, this premise is based upon an assumption that there are legitimate reasons to justify increased costs, when they do not exist. The opposite could in fact be true. If a compounded medication that is easier for the pet owner to administer is significantly more expensive (due to starting with finished goods) than a bitter FDA approved human health tablet, the pet owner may be forced to choose the FDA approved drug, only to give up when the animal repeatedly refuses the medication. This makes cost a factor in having to choose a less palatable option that may not be in the best interest of the patient. As noted elsewhere in our comments, our strong belief, which is supported by data and available scientific evidence, is that compounding from bulk increases safety by increasing accuracy, stability and palatability to support administration compliance. (A medication that cannot be administered to the animal patient is neither safe nor effective.)

(c) In all cases FDA-approved finished products are more expensive than the cost of the API contained in such finished drug products and often the price differential is shockingly high. This is understandable as API is an ingredient in the finished drug and the price of a finished drug product must account for the significant costs and expenses of developing, testing and marketing such drugs. Prices can also reflect the benefit of the drug. For example, a groundbreaking chemotherapy drug can be priced higher because it ultimately saves lives which saves health care costs and significantly adds societal value. In addition to increased API costs, requiring finished goods be used significantly increases labor costs due to the time necessary to open the capsules, grind the tablets or extract the liquids and results in more waste and increased generation of dust and particulates thereby requiring additional cleaning and decontamination.

(d) We are deeply concerned that this increase in price will make many commonly used animal health drugs beyond the means of pet owners. In our current shaky economic times, few people have discretionary funds to spend on medication for their pets. As a pharmacy serving hundreds of thousands of pet owners a year, we hear of many hardship cases when the costs of drugs are increased only a few percentage points. We believe that if GFI #256 is finalized to require compounding from finished drug product then scores of pet owners will be forced into the position of either letting their pets suffer with untreated diseases and

conditions or euthanizing their pets. Given the great emotional and spiritual value pets bring to individuals and society as a whole this choice should be unacceptable.

IV. The Definition of "Copy" is Extremely Limited and Will Create Unwarranted Administrative Burdens on Veterinarians

(a) Section A of GFI # 256 prohibits a veterinarian from prescribing, and a compounder from preparing, a compounded medication made from bulk drug substance intended for a specific patient if that compounded medication is a copy of a marketed, FDA-approved, conditionally approved, or indexed drug *unless* the veterinarian documents the medical rationale for why the compound will produce a clinical difference in the patient compared to the FDA-approved product. As noted above, while we agree that **exact copies** of FDA-approved drugs should not be compounded, we are not supportive of provisions requiring a veterinarian to justify their medical rationale. These administrative burdens do not improve patient safety and would significantly burden veterinarians whose time available to treat patients is already limited. We believe that to be considered an exact copy a compounded medication would need to contain the same API at a concentration of +/- 10% of what is available in the FDA-approved product, be in the same dosage form given by the same route of administration, with the same flavor, and be in the same or easily substitutable package size as the FDA-approved commercially available product. In essence, a compounded item would need to be exactly the same or have only a slight variation in strength or excipients when compared to the FDA-approved commercially available product. We note that in many instances flavorings are necessary in order to assure compliance with a drug regimen. If a patient refuses an unflavored drug, or is allergic to natural flavors contained in a flavored drug, an alternatively flavored drug should be an acceptable substitution without constituting a copy.

(b) GFI #256 proposes a very broad range of attributes a compounded item could have and still be considered a copy of a commercially available, FDA-approved product. This definition is so broad, in fact, that veterinarians will be required to provide their medical rationale for the need of the compounded medication more often than not. For example, if an FDA-approved commercially available product contains the desired API and exists in a tablet form for use in human patients, in order for a veterinarian to issue a prescription for an oral liquid compound containing that API for an animal patient, the veterinarian would need to document the medical justification for why that animal patient would clinically benefit from taking the compounded oral liquid, flavored for animal compliance, instead of being treated with the FDA-approved human health tablet. Even though the benefit of the animal using the compounded medication over the FDA-approved product is obvious to the veterinarian, compounding pharmacist, and pet owner, in an example like this the veterinarian would still be required to document their clinical justification. This type of documentation, if it goes beyond their normal course, only causes unnecessary administrative burdens on veterinarians who are already under tremendous pressure and does nothing to improve safety or protect drug approval, the purported basis of this Guidance.

V. The Rules and Standards for Producing Compounded Drugs for "Office Stock" Should Not Differ Than Those Of "Patient Specific" Drugs

(a) Dispensing for office use is a pharmacy practice, regulated by state boards of pharmacy, in which a pharmacist receives an order from a licensed prescriber for a specified medication, and then dispenses that medication to that prescriber for use in treating their patients. The key component of this practice is the prescriber-pharmacist relationship that exists at the time the order is being placed. Under no circumstances is the pharmacist dispensing medication without that relationship with the prescriber who is directly involved in treating patients.

(b) Veterinarians perform medical procedures and treat emergencies 24/7, which necessitate keeping medications in stock in order to perform those procedures, many of which are not planned in advance. In addition, some veterinarians are mobile and need the ability to keep medications in trucks to take to their patient, whether at a farm, stable or zoo, because some animals are not easily moved into a clinic or hospital environment for treatment. Having the ability to treat a sick patient immediately can speed the healing process, reduce discomfort, or, in an emergency, save a life. Explaining to pet owners of a dog or that they cannot start treatment of an antibiotic to treat their infection for 1-3 days or more because the medication must be prescribed, compounded, then delivered while their pet continues to suffer is not good medicine. At most, a delay in treatment could mean the death of a beloved pet.

(c) FDA's position that animal drugs compounded for veterinarian office stock pose a greater risk to animal patients than compounded medications prepared from FDA-finished product or those provided pursuant to a patient-specific prescription is unfounded. There is no evidence to support this position. The vast majority of states allow veterinarians to obtain office use animal drug compounds. Veterinarians are highly trained medical professionals who deeply care for and act in the best interests of their patients. In a recent survey of veterinary offices, 88% of respondents said that the ability to order and maintain office stock of compounded medications was extremely important or very important to their practice and their patients' health and medical outcomes and an additional 8% said it was somewhat important. Our strong view is that when 96% of veterinarians belief a practice is important to a patient's health then FDA should not substitute their judgment for the medical judgement of veterinarians and the regulations in a vast majority of states.

VI. The Proposed Standards for Qualifying to be Nominated for the "Positive List" Together With the "Negative List" May Disqualify Many Meaningful Candidates the Should Be Eligible for Nomination

(a) GFI #256 proposes that in order to compound animal drugs from bulk drug substances for use as office stock, the bulk drug substance must be listed on FDA's "List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals or Antidotes for Food Producing Animals." This list is commonly referred to as the "positive list." GFI #256 also proposes a list of eleven drug substances (the "negative list") which are proposed as prohibited from

being used in compounds for office use. In addition to requiring an expansive amount of information that in many ways is analogous to a new drug application, the nomination process outlined by FDA for the positive list has criteria that disqualifies a significant number of bulk ingredients currently in use from even being nominated. Shockingly these hurdles are the exact opposite of those that FDA specifies for human health compounding. We cannot understand why FDA believes that the risks posed by animal health compounding are greater than those of drugs compounded for humans.

(b) Many of the APIs on the negative list have been safely and effectively used by veterinarians for more than twenty years. The negative list contains drugs that make it difficult or impossible to start with finished product thus unnecessarily and unjustifiably eliminates office use orders for drugs using these APIs. The issues created by the negative list include: the quantity of finished product needed (in the case of Dexamethasone or Enrofloxacin this could be hundreds of tablets); the size of the finished compound (in the case of Budesonide or Gabapentin, a compounded capsule may be 5 times larger than a compounded tablet); and the appropriateness of the finished product for use as a starting material (in the case of Itraconazole, FDA-approved finished product is a cyclodextran coated bead that could not possibly be used to make an eye drop or ointment), and overriding many years of veterinarians' diagnostic and therapeutic experience by stating that a different drug should be used initially, and only upon failure can the veterinarian prescribe the desired treatment (Chloramphenicol, Idoxuridine).

(c) summary, we are opposed to using a "positive" and "negative" list at all (except as noted in VI.e), as it will drastically change the way veterinarians are treating their patients today. Veterinarians should determine (i) what medications are clinically appropriate to treat their patients, including when to order or prescribe a compounded medication, (ii) which of those medications they need on hand for their particular population of patients, and (iii) what documentation in their practice management systems is required to ensure a high standard of care. Most of the animal health orders we receive today are patient specific. However, we are in support of office use, as the veterinarian is responsible for deciding how best to treat their particular patients in their particular community. Although we agree with FDA that the items currently proposed on the positive list are some of the most important for a veterinarian to have on hand, and are unavailable as finished goods, this list is not all inclusive. And currently the majority of states permit office use for all compounded medication. Restricting access to a "positive" list, and restricting office use from a "negative" list, are most certainly some of the most worrisome provisions in the draft Guidance, and will most certainly cause unnecessary suffering and death.

(d) There are also substantial questions as to how the positive list process would work that are not addressed in GFI #256. Is FDA going to act, as they did in human health 503B, to suggest office use will be permitted for all animal drugs as they consider nominations? Will they use a format similar to the list 1, list 2 and list 3 format? It is still unclear how these nominations will be considered and by whom, and whether the individuals making those decisions will include stakeholders from practicing veterinarians to compounding pharmacists that specialize in animal

health, rather than with conflicted members from the pharmaceutical industry. We are interested in any plans to make the process more efficient than it has proven for 503Bs. We take no comfort that without a statute, as there is no indication of the process FDA will use in considering what medications FDA to include or exclude.

(e) We are supportive of the creation of a positive list of bulk drug substances that can be used to compound drugs for euthanasia, depopulation, and as poison antidotes for food animal species. Compounding from bulk in food-producing animals is medically necessary for these purposes when use of an FDA-approved product per label or in an extra label fashion is not feasible. Veterinarians must also be able to legally maintain sufficient quantities of these compounded preparations in their office for urgent administration needs or emergency situations. Without access, animals may die before the medication could be delivered (e.g., use of methylene blue to treat nitrate toxicosis in cattle). We recognize veterinarians' need to ensure food safety, maintain required records, and label drugs appropriately, as required under FDA's extra label drug use rules. We support the use of a positive list in this context because the necessary bulk drug substances are few in number, easily identified, and create a bright line for food-producing animals.

VII. A Robust Compounding Market Encourages Rather Than Discourages NDA-filings

(a) GFI #256 proposes that one of the reasons this Guidance is needed is because the use of compounded medications discourages pharmaceutical companies from taking new drug products through the new drug approval process. In reality, there is strong evidence of the opposite. Compounded medications are prepared in response to the requests of prescribers looking to meet the unique needs of patients whose medication therapy cannot be met with FDA approved commercially available drugs. Compounders do not create new active pharmaceutical ingredients – they tailor existing therapeutics to strengths, dosage forms, or flavors that meet the needs of individual patients or small populations of patients with similar needs. There are medications we prepare in more than 7 different dosage forms and more than 250 strengths and 30 flavors. There would be no way for a manufacturer to meet those needs. When the number of patients in need of a specific compounded preparation increases, it acts as a strong signal that there is potential market of patients whose medical needs cannot be met with existing drugs. When the market becomes particularly robust it signals to pharmaceutical companies that a particular compound is needed and that investment of the significant funds necessary to pursue an NDA-approval is likely to be worthwhile.

(b) There are multiple examples where pharmaceutical companies have recognized this signal and initiated the process of taking a compounded item through the new drug approval process. In 2008 FDA approved Vetoryl®, a capsule formulation of trilostane, a treatment for Cushing’s Disease that had been provided by compounders for many years. Prior to receiving FDA approval as Mirataz® in 2018, mirtazapine transdermal gel had been provided by compounders as a unique formulation to deliver mirtazapine to cats. Our perspective is that industry is looking to compounding trends for ideas, and that this industry is actually helping

the pharmaceutical industry, not hurting it, by exposing areas of opportunity in the marketplace that drug manufacturers can use as an incentive for taking drugs through the new drug approval process. Recall that Charles Pfizer, Eli Lilly, Edwin Squibb and Robert Upjohn were all compounding pharmacists.

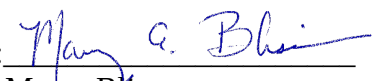
VIII. Conclusion

Wedgewood Pharmacy is surely the largest single provider of compounded medication to treat animal patients whose needs cannot be met by FDA-approved finished goods. We do this at the direction of a licensed veterinarian, under the rigorous regulations of every state where we ship, and in compliance with USP's rigorous quality standards. We strongly support the quality standards and state regulations that ensure patient safety. GFI #256, as proposed, increases restrictions and administrative burdens on veterinarians and pharmacists, and decreases access to patients for medication that is deemed to be important or very important to 98% of veterinarians in the U.S. We encourage reviewers to get in touch with the needs of the practicing veterinarians and compounding pharmacists; to study the excellent safety record for what are millions of doses of compounded medication for animal patients every year from veterinarians and thousands of pharmacies; and to appreciate that cost is a matter of life and death for animals when caregivers are paying out of pocket (as is almost always the case). We understand that pharmaceutical manufacturers have a right to drug approval and the patents and protections that come along with that and see that they are enjoying exceptional growth and prosperity even during COVID.

Contrary to what industry lobbyists may claim, we take care not to prepare copies of commercially available drugs and so do the compounding pharmacists we know. As an industry, we work with veterinarians to solve problems for patients that are difficult to treat. If this draft Guidance takes effect and is enforced without challenge, that may afford some benefits (however marginal) for pharmaceutical manufacturers, who can squeeze out another fraction of a percent of revenue or profitability by forcing veterinarians and compounding pharmacists to compound with finished goods (despite their lower quality). But that infinitesimally small benefit for pharmaceutical company profit will be dwarfed by the terrible costs suffered by tens of thousands of veterinarians and millions of animal patients and their caregivers who are happier and healthier today thanks to the essential service that compounding pharmacists are now able to provide safely and affordably. Accordingly, and for all the reasons we outline above, GFI #256 must be withdrawn.

Very truly yours,

Wedgewood Village Pharmacy, LLC

By: 

Marcy Bliss
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