FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS

VIA EMAIL CONFIRMED DELIVERY

July 30, 2024

Ms. Shauna M. Doherty
Pharmacist-In-Charge
Precision Equine LLC
5301 Young St
Bakersfield, CA 93311-8978
shauna.doherty@precisionpharmacy.com

Reference: CMS 688994

Dear Ms. Doherty:

U.S. Food and Drug Administration investigators inspected your facility Precision Equine LLC, located at 5301 Young Street, Bakersfield, CA, from August 23, 2023, through September 22, 2023. During the inspection, the investigators noted deficiencies in your practices for producing animal drugs and issued Form FDA 483.[1] The investigators also discussed the circumstances under which you produce animal drugs from bulk drug substances and distribute them, including drugs for food-producing animals, copies of FDA-approved products, and office stock compounded without patient-specific prescriptions. You responded to the inspection in writing on October 16, November 15, December 15, 2023, January 15, and February 15, 2024.[2] We have reviewed your responses. Although your responses addressed the objectionable practices and conditions related to drug quality described on the Form FDA 483, they did not specify changes to the circumstances under which you intend to produce and distribute unapproved new animal drugs from bulk drug substances. Therefore, we are not able to review the adequacy of your response with respect to the introduction into interstate commerce of unapproved new animal drugs.

[1] Form FDA 483 was issued September 22, 2023. An amended Form FDA 483 was sent by mail (cover letter dated September 26, 2023), reflecting the name of an investigator inadvertently left off the original Form FDA 483.
[2] You also referenced corrective actions in an email dated July 19, 2024, and committed to reviewing your procedures related to collection of medical rationales and ensuring that the amount of drug is appropriate for the size of any group populations by August 15, 2024. You stated that you would provide monthly updates. We will review these updates and any other information you provide.

Division of Pharmaceutical Quality Operations IV
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A. Unapproved New Animal Drugs

You compound drugs for animals from bulk drug substances (BDS). From May 23 to August 23, 2023, you filled approximately (b) (4) prescriptions or orders for animal drugs. Most of your products are compounded using BDS.[3]

Animal drugs compounded from BDS are new animal drugs as defined in section 201(v) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) because they are not generally recognized as safe and effective by experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs. Under section 512 of the FD&C Act, to be legally distributed, a new animal drug requires an approved new animal drug application, conditionally approved new animal drug application, or a listing on the Index of Legally Marketed Unapproved New Animal Drugs for Minor Species. Compounded drugs do not go through any of these pre-market review processes. Although compounded human drugs are, under certain circumstances, exempt from the human drug approval requirement in section 505 of the FD&C Act, no comparable exemption from section 512 exists for animal drugs. Distribution of animal drugs compounded from BDS without an approval or index listing violates the FD&C Act.

In addition, the drug products you compound from BDS are intended for conditions not amenable to diagnosis and treatment by individuals who are not veterinarians. Therefore, adequate directions for use cannot be written so that a lay person can use these products safely for their intended uses. Consequently, their labeling fails to bear adequate directions for their intended uses as required under section 502(f)(1) of the FD&C Act, and they are not exempt from this requirement by any other statutory provision or regulation.

Although compounded animal drugs lack required approval or index listing, the FDA acknowledges there are some situations in which no FDA-approved or indexed drug can treat an animal, and a drug compounded from BDS may be medically appropriate. FDA's Guidance for Industry (GFI) #256, "Compounding Animal Drugs from Bulk Drug Substances" identifies the circumstances under which the FDA does not intend to take enforcement action against drugs compounded from BDS. The guidance also generally describes our enforcement priorities with respect to compounded animal drugs. Our priorities for enforcement include animal drugs that are intended for use in food-producing animals; copies of marketed FDA-approved or indexed drugs; or compounded without a patient-specific prescription (i.e., office stock).

Drugs for Food-producing Animals

Use of drugs compounded from BDS to treat food-producing animals and free-ranging wildlife species risks exposing humans to potentially harmful residues in the animals' edible tissues because these drugs have not been reviewed to determine human food

[3] The FD&C Act permits the compounding of animal drugs made from FDA-approved animal or human drugs, provided the conditions for legal extralabel use described in the FD&C Act and FDA's extralabel use regulations are met. Sections 512(a)(4) and (5) of the FD&C Act [21 U.S.C. § 360b(a)(4) and (5)] and 21 CFR part 530.

safety. According to your product labels, compounding log, and prescriptions, you compound products for use in food-producing animals, for example:

- Prescription no. (b) (6), (b) (7)(C): Dexamethasone Sodium Phosphate in Water, Injectable, 24mg/mL, for use in deer

- Prescription no. (b) (6), (b) (7)(C): Toltrazuril in Oil 2.2mg/10mL (220 mg/mL) Suspension, for use in deer

- Prescription no. (b) (6), (b) (7)(C): Xylazine in Water, injectable, 333 mg/mL, for use in goats. Although prescription (b) (6), (b) (7)(C) asserts that the goats are non-food producing, it does not provide any further information about the goats or their uses. The label includes a withdrawal time. A withdrawal time is intended to ensure that food products from a treated food-producing animal are safe to enter the food supply by establishing sufficient time from when the animal was last treated with the drug to when the animal is milked or slaughtered for food. Based on the labeled withdrawal time, this prescription appears to be for food-producing animals.

Copies of Approved or Indexed Products

The FDA considers an animal drug compounded from a bulk drug substance to be a copy of an FDA-approved or indexed product if it has the same active ingredient or active moiety and is given by the same route of administration ("ROA"). In addition, the FDA considers a combination drug product to be a copy if any of its active ingredients is approved in the same ROA. Compounded copies of approved or indexed animal drugs are an FDA priority for enforcement because they may expose animals to drugs produced under lesser quality controls compared to the approved/indexed products and reduce incentives for firms to seek approval or indexing of their drugs. You compound copies of approved products, for example:

- Prescription no. (b) (6), (b) (7)(C): Azithromycin in Oil, 200 mg/mL Suspension, 2000 mL for 8 horses "in breeding barn"
    - Your azithromycin (oral ROA) is a copy of multiple FDA-approved drugs containing azithromycin for oral administration, including suspensions as well as tablets. Among the approved suspensions are NDAs 050693 and 050710, and ANDA 205666. Your records state that patients "would require too many commercial tablets," but do not address why the approved suspensions cannot be used.

- Prescription no. (b) (6), (b) (7)(C): Fenbendazole in Oil 20% Suspension, 2000 mL for horses "in Mare Barn"
    - Your fenbendazole suspension (oral ROA), is a copy of approved orally administered drugs intended for use in horses containing fenbendazole, including an oral suspension, NADA 128-620, an oral paste, NADA 120-648, and granules for top dressing of feed, NADA 121-473. Your records state that the patient "isn't compliant w/ commercial product. [Too much

volume required]" but do not address why the volumes required for all of these approved products would be inappropriate for each of the horses to be treated. For example, NADA 128-620 is a 10% suspension, 1000 mL bottle, and is approved for horses. The labeled dose of this product for horses is 5-10 mg/kg. At the higher end of the dosage range, an average 500 kg horse would require 50 mL of the approved product, which is generally an acceptable amount to administer orally to a horse.

- Prescription no. (b) (6), (b) (7)(C) Ivermectin/ Praziquantel in Oil 10mg/45mg Per mL Apple-Flavored Suspension, 600 mL for "6 horses in barn 1"
    - Your ivermectin and praziquantel combination (oral ROA) is a copy of approved oral paste products containing both these ingredients, including NADA 141-214 and NADA 141-215. In addition, these active ingredients are available separately in approved products, including NADA 134-314 (ivermectin paste) and NADA 111-798 (praziquantel tablets). Your records state that the patients "would require too much volume of commercial products" but do not address why the volumes required would be inappropriate for each of the horses to be treated or whether the approved products could be used separately instead of in combination.

Office Stock

"Office stock" refers to compounded drugs ordered by a veterinarian without a patient-specific prescription to keep on hand in the veterinary clinic or office to administer or dispense to patients. When drugs are compounded for use as office stock, and are therefore readily available for use, the products potentially expose large numbers of animals to drugs of unproven safety, effectiveness, and quality. You compound drugs for office stock, for example:

- Prescription no. (b) (6), (b) (7)(C) Praziquantel/ Pyrantel Pamoate/ Fenbendazole in Oil 45.4mg/ 45.4mg/ 50mg Per mL Suspension, 100 mL "to treat worms in equine."

- Prescription no. (b) (6), (b) (7)(C) Xylazine in Water 333 mg/mL Injectable 60 mL for animal identified as "(b) (6), (b) (7)(C) (Horse)." Although this prescription lists a specific patient, the animal owner and veterinarian are the same individual and the amount dispensed appears to exceed the amount needed to treat a single horse using the labelled directions. At the higher end of the dosage range (1-2 mg/kg), a 500 kg horse would require 5-10 mL of the approved product, or 1.5-3 mL of the compounded product. Thus, it appears this product is intended to be distributed to more than one horse by the veterinarian who ordered it.

B. Drug Quality Violations

All animal drugs produced from bulk drug substances are subject to the FD&C Act's Current Good Manufacturing Practice (CGMP) requirement, section 501(a)(2)(B), and

our inspection determined that you are not in compliance with that requirement. We noted that your firm sells office stock which potentially exposes large numbers of animals to drugs which do not meet the CGMP quality standard set by the FD&C Act. We further noted that your firm produces copies of FDA-approved products from bulk drug substances but does so without the same CGMP controls which ensure their quality. For example, unlike FDA-approved products, you fail to test the strength/potency of each batch,[4] perform stability testing,[5] and establish, follow and validate all aseptic and sterilization processes to prevent microbial contamination.[6]

Additionally, unknown yellow stains were observed by the FDA on the HEPA filter inside the ISO 5 laminar air flow hood (LAFH) in the Sterile Non-Hazardous Drug Suite, which is used for producing sterile animal drugs.[7] However, your response does not contain an investigation of the root cause. It is critical to perform comprehensive investigations into product failures, to ensure identity, strength, and quality of drug products before they are dispensed and administered.

In your written responses, you indicated that you intended to compound drugs in accordance with USP General Chapters <795> and <797> and not CGMP because you are a pharmacy and do not believe you are subject to CGMP. As described above, unlike human drugs compounded in accordance with section 503A, the FD&C Act does not exempt pharmacies that produce animal drugs from bulk drug substances from CGMP. The Act's CGMP requirement in section 501(a)(2)(B) applies to anyone who manufactures or processes animal drugs.

Conclusion

All of the animal drugs you produce from BDS violate the FD&C Act's requirements for approval/indexing, adequate directions for use, and CGMP.[8] We do not consider you a low priority for enforcement action as described in GFI #256. The specific drugs identified above are examples that represent general practices at your firm.

This letter is not intended to be an all-inclusive statement of violations that may exist in connection with your products. You are responsible for investigating and determining the causes of any violations and for preventing their recurrence or the occurrence of other violations. It is your responsibility to ensure that your firm complies with all the requirements of federal law, including FDA regulations.

In addition, we offer the following comments:

- As described in GFI #256, the FDA has reviewed information concerning specific antidotes, anesthetics, and sedatives for food-producing animals and free-ranging wildlife for which the FDA generally intends to exercise enforcement

[4] *See* 21 CFR 211.165(a).
[5] *See* 21 CFR 211.137 and 211.166.
[6] *See* 21 CFR 211.113(b).
[7] *See* 21 CFR 211.67; *See also*, FD&C Act, section 501(a)(2)(A) [21 U.S.C. § 351(a)(2)(A)].
[8] Section 512 of the FD&C Act [21 U.S.C. § 360b], 502(f)(1) of the FD&C Act [21 U.S.C. § 352(f)(1), and section 501(a)(2)(B) of the FD&C Act [21 U.S.C. § 351(a)(2)(B)] (see also 21 CFR parts 210 and 211).

discretion. These drugs are on the List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species.[9] As discussed above, you produce drugs containing dexamethasone sodium phosphate and toltrazuril for use in deer and xylazine for use in goats. The FDA reviewed information on xylazine and did not include it on the list because there are FDA-approved drugs containing the same active ingredient, in the same or similar dosage form, that can be used in an extralabel manner. The FDA has not reviewed dexamethasone sodium phosphate or toltrazuril for use in deer.

- The FDA recognizes that there are some circumstances in which the treating veterinarian determines that a particular patient cannot be treated with an FDA-approved product and needs a compounded copy with a specific difference from the FDA-approved drug. GFI #256 recommends that pharmacies obtain a medical rationale from the treating veterinarian that explains how the prescribed compounded product makes a clinical difference for the patient. This statement should explain why the approved drug cannot be used by identifying which characteristic of the approved/indexed drug is unsuitable for the individual patient and how that characteristic has been altered in the prescribed compounded drug so as to create a clinical difference for the individual patient. If there are multiple approved products that vary in dosage form, strength or formulation, medical rationales should address each approved product. A general statement of "Patient Noncompliance" does not explain why the approved drug should not be used because it does not identify which characteristic(s) of the approved/indexed drugs is unsuitable for the individual patient and how that characteristic has been altered in the prescribed compounded drug so as to create a clinical difference for the individual patient.

- We note that you document rationales[10] for using BDS as the source of the active ingredient instead of approved products using a table that maps BDS you use to make various specified dosage forms to justification codes, each of which contains a general description. We are concerned that these rationales do not explain why an FDA-approved/indexed drug cannot be used, particularly when the compounded drug is a copy of more than one FDA-approved drug. As examples: the justification "[e]xcipient in approved product affects flavor and/or texture making compound unacceptable" neither specifies the excipient nor explains the specific underlying problem (bitterness, grainy texture, etc.). You

[9] Additionally, drugs which the FDA is considering for placement on the List of Bulk Drug Substances for Compounding Drugs for Use in Food-Producing Animals or Free-Ranging Wildlife Species, and which the FDA recommends remain available during FDA's review, are found on this List of Bulk Drug Substances Currently Under Review.

[10] As stated in GFI 256, it is recommended that the "compounder has determined and documented the reason(s) why none of these drugs can be used as the source(s) of the active ingredients."

also have several justifications that generally state the conclusion "[i]t is not possible to compound [this dosage form] from [another dosage form]," but do not state the underlying reason. Similarly, the justification "Preparation would require too many tablets/capsules/vials of the approved product," does not explain how many doses of the approved product would be required compared to the compounded product.

- While most animal patients' needs for compounded drugs can be met with patient-specific prescriptions, the FDA recognizes that in some cases an animal drug is urgently needed, and the time needed to compound a drug in response to an individual patient prescription may result in animal suffering or death. The FDA has reviewed information concerning certain compounded drugs veterinarians need for urgent treatment. These drugs are on the List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals.[11] As noted above, you have dispensed drugs containing xylazine and a combination drug containing praziquantel, pyrantel pamoate, and fenbendazole for use as office stock. The FDA reviewed information on xylazine and did not include it on the list because there are FDA-approved drugs containing the same active ingredient, in the same or similar dosage form, that can be used as labeled in horses or FDA-approved products that can be used in an extralabel manner. The FDA has not reviewed the combination of praziquantel, pyrantel pamoate, and fenbendazole for use in horses.

Within thirty (30) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to address any violations. Please include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. This letter notifies you of our concerns and provides you an opportunity to address them. If you believe your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration. If you cannot completely address this matter within thirty (30) working days, state the reason for the delay and the time within which you will do so.

Please send your electronic reply to ORAPHARM4_Responses@FDA.HHS.GOV or mail your reply to:

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV
U.S. Food and Drug Administration
19701 Fairchild Road
Irvine, California 92612-2506

Please identify your responses with the unique identifier: **CMS 688994**

[11] Additionally, drugs which the FDA is considering for placement on the List of Bulk Drug Substances for Compounding Office Stock Drugs for Use in Nonfood-Producing Animals, and which the FDA recommends remain available during FDA's review, are found on this List of Bulk Drug Substances Currently Under Review.

If you have questions regarding the contents of this letter, please contact Andrew Haack, compliance officer by telephone at 206-340-8212 or email at Andrew.Haack@fda.hhs.gov.

Sincerely,

CDR Steven E. Porter, Jr.
Director, Division of Pharmaceutical Quality Operations IV

SP: ah