U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III
300 River Place, Suite 5900
Detroit, MI 48207
Telephone: (313) 393-8100
Fax: (313) 393-8139
www.fda.gov

FDA U.S. FOOD & DRUG ADMINISTRATION
OFFICE OF REGULATORY AFFAIRS
OPQO DIVISION OF PHARMACEUTICAL QUALITY OPS 3

June 10, 2024

UPS NEXT DAY
SIGNATURE REQUIRED

Nicholas Kirkpatrick, PharmD
Pharmacist In Charge
Wickliffe LLC
4340 Georgetown Rd
Lexington, KY 40511-9115

nick.kirkpatrick@wicklifferx.com

Reference Case: 685939

Dear Dr. Kirkpatrick:

U.S. Food and Drug Administration (FDA) investigators inspected your facility Wickliffe LLC, located at 4340 Georgetown Road, Lexington, KY 40511-9115 from August 21, 2023, through September 15, 2023. During the inspection, the investigators noted deficiencies in your practices for producing animal drugs and issued an FDA Form 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 5, 2023, November 15, 2023, December 15, 2023, and January 15, 2024. We have reviewed your responses. Although your responses addressed the objectionable practices and conditions related to drug quality described on the FDA Form 483, they did not indicate any 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.

A. Unapproved New Animal Drugs

You compound drugs for animals from bulk drug substances (BDS). From May 23, 2023 to August 18, 2023, you filled approximately (b) (4) prescriptions or orders for animal drugs. Most of your products are compounded using BDS.[2]

[1] An FDA Form 483 was issued September 15, 2023. An amended Form FDA 483 was sent by mail (cover letter dated September 28, 2023).
[2] 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.

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 layman 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, 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. In light of these situations, FDA's Guidance for Industry (GFI) #256, "Compounding Animal Drugs from Bulk Drug Substances" identifies the circumstances under which FDA generally 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; are copies of marketed FDA-approved or indexed drugs; or are 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 harmful residues in the animals' edible tissues because these drugs have not been reviewed to determine human food safety. According to your product labels, compounding log, and prescriptions, you compounded the following products for use in food-producing animals:

- Prescription # (b) (4) : Toltrazuril Suspension 50mg/mL - 250mL, office stock for bovine use
- Prescription # (b) (4) : Tolazoline Injectable 100mg/mL - 100mL, for use in goats

Copies of Approved or Indexed Products

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 can be given by the same route of administration ("ROA"). Compounded copies of approved or indexed 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:

- Prescription # (b) (4) : Azithromycin in Oil Suspension 50mg/mL - 30mL
    - Your azithromycin (oral ROA) is a copy of multiple FDA-approved drugs including NDA 050710, which is an oral ROA drug containing azithromycin. Although your record stated that "[patient] cannot be safely pilled" and "Patient Noncompliance," we note that this approved product is not a pill, and it is not clear why the patient would be noncompliant with an approved product that is also administered in liquid form.

- Prescription # (b) (4) : Pergolide Mesylate Powder 1mg/0.25TSP - 60 scoops
    - Your pergolide (oral ROA) is a copy of the FDA-approved drug, Prascend (NADA 141-331, 1mg pergolide mesylate tablets). Although your record stated that you compounded this product because "Concentration Adjustment Necessary," we note that there is no concentration difference between administering a 1 mg scoop of the compounded powder and administering the 1 mg FDA-approved tablet.

- Prescription # (b) (4) : Cyclosporin Capsule 110 mg
    - Your cyclosporin (oral ROA) is a copy of multiple FDA-approved drugs including (NADA 141-218, NADA 141-329, and ANADA 200-692). The approved products are available in 10 mg capsules, 100 mg capsules, and 100 mg/mL liquid. Although your record stated that you compounded this product because "Concentration Adjustment Necessary," the same dose is available with a 10 mg approved capsule plus a 100 mg approved capsule (total 110 mg) or 1.1 mL of the approved (100 mg/mL) liquid.

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. For the time period of our review, over (b) (4) prescriptions had "human" recorded as the species. During the inspection, you stated that you do not dispense any drugs for human use but do not routinely ask for the species in which office stock prescriptions will be used. For example, you compound the following drugs for office stock:

- Prescription # (b) (4) : Phenylbutazone (Alfalfa) Powder 1gm/TSP - "human" species
- Prescription # (b) (4) : Doxycycline Powder 5gm/TBSP - 14 scoops – "human" species
- Prescription # (b) (4) : Phenylbutazone (Apple) Powder 1gm/TSP - 500 scoops –

"human" species

Additionally, for the time period of our review, the investigators observed prescriptions for a "herd" of animals that appear to be intended for larger numbers of animals than written on the prescription, indicating their use as office stock. Numerous compounded drugs were dispensed for the same group[3] of 10 horses over a 90-day period. These drugs included: calcium levulinate/magnesium sulfate/thiamine, cyproheptadine, dantrolene, doxycycline, estradiol cypionate, flunixin meglumine, isoxsuprine, medroxyprogesterone acetate, methocarbamol, minocycline, misoprostol, omeprazole, pergolide mesylate, ponazuril, sucralfate, toltrazuril, and tryptophan. The drugs compounded for this "herd" also included quantities of drugs that would be expected to exceed the beyond use date of these drugs if used as directed:

- Prescription # (b) (4) : Methocarbamol 2.5gm/TBSP Powder - 100 scoops
    - This prescription is for a group of 10 horses with instructions to give 1 scoop orally twice daily. (b) (4) 100-scoop units were filled from 7/25/2023 to 8/18/2023. This amounts to a (b) (4) supply for 10 horses dosed at 1 scoop twice daily.
    - There were additional methocarbamol oral powder prescriptions filled for the same herd of 10 horses including (b) (4) 100-scoop units with a beyond use date of 12/5/2023 dispensed between 6/13/2023 and 7/14/2023. This would amount to an additional (b) (4) supply for 10 horses dosed at 1 scoop twice daily.
    - Altogether, these prescriptions amount to a (b) (4) supply. The period from the first prescription (6/13/2023) to the latest beyond use date (1/22/2024) is 223 days. If these prescriptions were only intended to be used in these 10 horses, treatment would be expected to exceed the beyond use date of these drugs.
- Prescription # (b) (4) : Pergolide Mesylate Powder 1mg/0.25TSP - 60 scoops
    - This prescription is for the same group of 10 horses noted above. A total of (b) (4) 60-scoop units of the pergolide oral powder ((b) (4) doses, (b) (4) supply for 10 horses dosed at 1 mg/day) were filled between 5/31/2023 and 8/18/2023.
    - The period from the first prescription (5/31/2023) to the latest beyond use date (1/13/2024) is 227 days. If these prescriptions were only intended to be used in these 10 horses, treatment would be expected to exceed the beyond use date of these drugs.

It is unlikely that this combination of drugs would be needed in the same population of 10 horses. Pergolide and cyproheptadine are used to treat pituitary pars intermedia dysfunction, which is a disease of older horses. However, many of the other drugs in this list including calcium levulinate/magnesium sulfate/thiamine, estradiol cypionate, medroxyprogesterone acetate, and tryptophan are typically used to modify behavior in younger performance horses. Additionally, dantrolene is typically used in younger performance horses for the treatment of exertional rhabdomyolysis.

B. Drug Quality Violations

All animal drugs are subject to the FD&C Act Current Good Manufacturing Practice (CGMP)

[3] All of the prescriptions were written for "(b) (4) ." (b) (4) is a veterinary practice.

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 that 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 that ensure their quality. For example, unlike FDA-approved products, you fail to test the strength/potency of each batch,[4] use a validated production process to ensure each individual unit meets strength, quality, and purity requirements,[5] and validate all aseptic and sterilization processes to prevent microbial contamination.[6]

Additionally, during the inspection on September 7, 2023, during aseptic filling of reserpine, brown residue was wiped off the bottom of vials that were introduced to the sterile hood for filling, and your root cause identified the most likely source of brown residue to be transfer of the residue from shared equipment ((b) (4)) that was used during production of a different drug (altrenogest) several weeks before on August 4, 2023.[7] Your response indicated that you had hired an outside expert to conduct a health hazard evaluation (HHE) to evaluate microbiological contamination risk and cross-contamination risk; however, your HHE did not directly evaluate the microbiological contamination risk as was indicated in your response. Additionally, you failed to address potential health risks for humans when handling the vials of the other distributed batch you identified as potentially affected. Altrenogest is a synthetic hormone that is intended to affect the reproductive system in animals, and therefore may present a human health hazard (e.g., pregnant women or women of childbearing age as accidental absorption could affect the menstrual cycle or pregnancy).

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 response, 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 who produce animal drugs from bulk drug substances from CGMP. The FD&C 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, 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.

---

[4] *See* 21 CFR 211.165(a).
[5] *See* 21 CFR 211.100(a).
[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], 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), and section 502(f)(1) of the FD&C Act [21 U.S.C. § 352(f)(1)].

This letter is not intended to be an all-inclusive statement of violations that may exist in connection with your product. 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, FDA has reviewed information concerning specific antidotes, anesthetics, and sedatives for food-producing animals and free-ranging wildlife for which FDA generally intends to exercise enforcement 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 toltrazuril for bovine use and tolazoline for use in goats. FDA has not reviewed information concerning toltrazuril or tolazoline for use in these species.

- 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. A general statement of "Patient Noncompliance" does not explain why the approved drug should not be used because it does not identify which characteristic 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 instead of approved products using a table that maps bulk drug substances 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 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

[9] Additionally, drugs which 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 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."

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, 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. 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 pergolide and methocarbamol for use as office stock. FDA reviewed information concerning pergolide and methocarbamol for use in horses and did not include them on the list because there is an FDA-approved drug 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.

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 address your reply via email to ORAPHARM3_RESPONSES@fda.hhs.gov

Attention: Brian D. Garthwaite, Ph. D.
Compliance Officer
U.S. Food and Drug Administration
Division of Pharmaceutical Quality Operations III

Your reply should reference case #685939 and include your FEI 3002992930. If you have questions regarding the contents of this letter, please contact Dr. Garthwaite at (612) 758-7132 or at ORAPHARM3_RESPONSES@fda.hhs.gov.

Sincerely,

Rebecca E. Dowd -S

Digitally signed by Rebecca E. Dowd -S
Date: 2024.06.10 15:01:22 -04'00'

Rebecca E. Dowd
Program Division Director
Division of Pharmaceutical Quality Operations III

[11] Additionally, drugs which 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 FDA recommends remain available during FDA's review, are found on this List of Bulk Drug Substances Currently Under Review.