U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

Office of Surveillance and Compliance
Division of Compliance, HFV-230
7519 Standish Place
Rockville, MD 20855

August 15, 2017

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Siobhan Ellison, DVM, PhD
President
Pathogenes, Inc.
15471 NW 112th Ave.
Reddick, FL 32686

Dear Dr. Ellison:

This letter concerns your firm's distribution of unapproved animal drugs for the prevention, mitigation, or treatment of Equine Protozoal Myeloencephalitis (EPM) in horses. Those drugs are Orogin tablet (decoquinate (b) (4) levamisole HCL (b) (4)), NeuroQuel tablet (levamisole HCL 550 mg), and Decoquinate Pellet (Decoquinate 0.018%).

As outlined in this letter, based on FDA's inspection and review of your literature, it appears that you are producing and distributing animal drugs that violate the Federal Food, Drug, and Cosmetic Act (FD&C Act). Further, you did not meet the requirements to distribute those drugs as investigational new animal drugs. Your correspondence with us demonstrates your misunderstanding or lack of knowledge about the requirements for animal drug approval under the FD&C Act and FDA regulations.

I. BACKGROUND AND BASIS FOR FDA ACTION

The U.S. Food and Drug Administration (FDA) conducted an inspection of your facility, Pathogenes, Inc., located at 15471 NW 112th Ave., Reddick, FL 32686, (b) (4) (b) (4) In addition, we reviewed your website at www.pathogenes.com on August 3, 2015, October 26, 2016, and April 14, 2017; Pathogenes' slide presentations available on slideshare.net as of March 30, 2017; your Pathogenes' blog at http://pathogenes.com/w/epm-blog/ on May 23, 2017; and your letter to FDA in response to the inspection ("response letter") (b) (4)

According to your website and various submissions you made to FDA,[1] Orogin is intended for treatment of clinical signs of EPM due to S. neurona infections in horses and NeuroQuel is intended for the treatment of residual or recurrent signs of inflammation due to EPM. The FDA inspection confirmed that these drugs have been manufactured (b) (4) Decoquinate pellets are a medicated feed that you manufacture using decoquinate 6%, which you told FDA investigators that (b) (4) Your intended use for this feed is prophylaxis for EPM in normal horses with a likelihood of relapse of clinical signs due to EPM.[2]

During the (b) (4) inspection, you reported to FDA investigators that as of (b) (4) you had distributed Orogin and NeuroQuel to treat approximately 585 horses, and Decoquinate 0.018% pellet to treat approximately 77 horses. Your records show that you sent them to veterinarians and other individuals in numerous states.

II. DISTRIBUTION OF UNAPPROVED NEW ANIMAL DRUGS

A. Orogin and NeuroQuel

Your products, Orogin and NeuroQuel are intended to prevent, mitigate or treat diseases in animals and therefore are drugs under section 201(g)(1)(B) of the FD&C Act [21 U.S.C. § 321(g)(1)(B)]. In addition, Orogin and NeuroQuel are considered new animal drugs under the FD&C Act because they are intended for a minor use, which is the intended use of a drug in a major species (cattle, horses, swine, chickens, turkeys, dogs, and cats) for an indication that occurs infrequently and in only a small number of animals or in limited geographical areas and in only a small number of animals annually.[3] Section 201(v) of the FD&C Act [21 U.S.C. § 321(v)].

To be legally distributed, a new animal drug must have an approved new animal drug application, conditionally approved new animal drug application, or index listing under sections 512, 571, and 572 of the FD&C Act [21 U.S.C. §§ 360b, 360ccc, and 360ccc-1]. Animal drugs that lack the required approval or index listing are considered "unsafe" and "adulterated" under sections 512(a) and 501(a)(5) of the FD&C Act [21 U.S.C. §§ 360b(a) and 351(a)(5)]. Introduction of an adulterated animal drug into interstate commerce is prohibited under section 301(a) of the FD&C Act [21 U.S.C. § 331(a)].

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[1] See Designations List, Minor Uses, Minor Species Drugs, www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/ucm125445.htm.

[2] Pathogenes Inc., "Decoquinate 0.018% Pellet, Evidence of Potential Clinical Benefit, Brief Protocol for exploratory study: Decoquinate Pellet Prophylaxis".

[3] See letters, Meg Oeller, DVM, Office of Minor Use and Minor Species, CVM, FDA to Siobhan P. Ellison, DVM, PhD, Pathogenes, May 7, 2012, (MUMS Drug Designation letter I-012092-I-0009-IR) and March 5, 2013 (MUMS Drug Designation letter I-012219-I-0007-IR).

B. Decoquinate Pellet

Your decoquinate pellet is an animal feed bearing or containing a new animal drug. To be legally distributed, an animal feed bearing or containing a new animal drug must be used and labeled in conformity with the approved application for the new animal drug.

There is an approved decoquinate 6% Type A medicated article for use in preparing animal feed, but that article is not approved for use in horses or to prevent or treat EPM. Because the drug was not used as described in the drug approval, the new animal drug contained in the feed (decoquinate) is considered "unsafe" and "adulterated" under sections 512(a)(1) and 501(a)(5) of the FD&C Act [21 U.S.C. §§ 360b(a)(1) and 351(a)(5)]. In addition, the animal feed containing the new animal drug is considered "unsafe" and "adulterated" under sections 512(a)(2) and 501(a)(6) of the FD&C Act [21 U.S.C. §§ 360b(a)(2) and 351(a)(6)]. Therefore, distribution of your decoquinate pellet product in interstate commerce is prohibited and violates section 301(a) of the FD&C Act [21 U.S.C. § 331(a)].

III. INVESTIGATIONAL EXCEPTION TO APPROVAL REQUIREMENT NOT MET FOR DISTRIBUTING ANIMAL DRUGS

Section 512(j) of the FD&C Act [21 U.S.C. 360b(j)] provides an exception to the approval requirement to permit the distribution of investigational animal drugs to conduct studies to support an application for approval, conditional approval, or index listing. To qualify for this exception the new animal drug must be for investigational use and must comply with the requirements in Title 21, Code of Federal Regulations (21 CFR), Part 511.

A. Failure to Establish an INAD

You communicated previously with the Center for Veterinary Medicine (CVM) about establishing investigational new animal drug files (INADs) for Orogin and NeuroQuel, and INAD file numbers were assigned (# I-012092 and # I-012219, respectively). However, you did not meet the regulatory requirements in 21 CFR Part 511 to establish INAD exemptions for Orogin and NeuroQuel.

You did not communicate with FDA about establishing an INAD file for your use of the decoquinate in the medicated feed you distribute.

B. Regulatory Violations Observed

1. You failed to submit to FDA a Notice of Claimed Investigational Exemption (NCIE) for a New Animal Drug prior to shipment of the new animal drugs for clinical tests in animals (21 CFR § 511.1(b)(4)(i)-(iv)).

Specifically, during the period from January 2013 through March 2016 you shipped to veterinarians and other individuals approximately 585 shipments of the investigational new animal drugs Orogin or NeuroQuel or both intended for the treatment of EPM. You failed to submit NCIEs prior to shipping these investigational new animal drugs for clinical tests in animals as required by 21 CFR 511.1(b)(4).

Soon after the inspection of your facility, you submitted to CVM several submissions of more than 1,000 pages, some of which you intended to be NCIEs. However, those NCIE submissions were not submitted prior to distribution and do not include all of the information required by the regulations. Those submissions do not identify the animal drug(s) shipped, the labeling and information sent to the investigator, and the quantity shipped or number of animals to be treated with the shipment.[4]

2. You represented that a new animal drug is safe or effective for the purposes for which it is under investigation (21 CFR § 511.1(b)(8)(iv)).

   Specifically, some examples of claims by your firm that the products are safe and effective include statements in your EPM Survival Guide, (Pathogenes Limited Edition), which FDA investigators obtained from you during the (b) (4) inspection:

   - "Orogin, has a remarkable record for treatment success and is more economical than less than effective therapies, thus saving many hundreds horses who would not be helped by other drugs or whose owners could not afford them." [Page 3]

   - "The anti-protozoal drug used in Orogin kills all strains of S. neurona SnSAG 1 strains that were tested in vitro. Horses that are effectively treated respond well clinically and show a reduction in SnSAG 1 antibodies." [Page 35]

   - "Decoquinate at low doses is effective in treating horses that have EPM, as we found in our studies." [Page 43]

   In your (b) (4) response letter, you stated that Pathogenes, Inc. will no longer give the EPM Survival Guide to veterinarians. We note however that presentation slides entitled "Survival Guide for Equine Protozoal Myeloencephalitis" are currently available on slideshare.net, along with other

[4] 21 CFR § 511.1(b)(4) requires that the NCIEs include among other things:
"(i) – The identity of the new animal drug.
(ii) – All labeling and other pertinent information to be supplied to the investigators . . .
(iii) – The name and address of each clinical investigator.
(iv) – The approximate number of animals to be treated (or if not available, the amount of new animal drug to be shipped)."

Pathogenes slide sets. Slides 15 through 20 from the Survival Guide make treatment recommendations for Orogin and NeuroQuel that vary depending on grading of the horse's clinical presentation. For instance:

- Slide 15, regarding stage 5 acute cases: "Down animals can respond to treatment. Those that do respond generally need an extended duration of levamisole HCl (10 days in Orogin followed by 14 days levamisole HCl). DMSO IV is useful. Sometimes dysphasic, NeuroQuel absorbs through mucous membranes, response in 3-5 days."

- Slide 17, regarding stage 2-5 chronic cases: "Orogin treatment response by day 5. Clinical signs resolve by day 10 but needed further NeuroQuel treatment…. Signs can recur after NeuroQuel discontinued. These cases usually respond to longer duration of NeuroQuel. Can repeat NeuroQuel, use every other day and move to every 3rd day. … May need prevention therapy with decoquinate."

- Slide 20, entitled "Treatable Presentations Diagnosed as EPM" summarizes treating with NeuroQuel and/or Orogin in different scenarios.

While other Pathogenes slide sets on slideshare.net and your continuing education course materials on your website acknowledge that your drugs are undergoing investigation and are not approved or "licensed" by the FDA, these same documents also include statements implying that the drugs you distribute are safe and effective and make treatment recommendations involving these products.[5]

As recently as May 2017, through your Pathogenes EPM blog, you continued to imply that the drugs you distribute are effective. For example, on page 7 you stated: "We found the clinical effects of levamisole HCl are surprisingly rapid"; and, "Clinically, the relative rapid return of wasted muscles in the top line, neck, and gluteal muscles of horses treated with levamisole HCl is appreciated. There is a rapid response of 'body sore' horses to levamisole HCl treatment." On page 8, you called levamisole a "Superdrug". Further, on page 11, you stated: "If all horses in our data set are treated with an anti-protozoal and immune modulating drug (we used decoquinate and levamisole in combination (Orogin)-- 93% of the S. neurona horses respond to treatment."

We remind you that to comply with the requirements for an investigational new animal drug that would provide an exemption for your unapproved drugs and therefore permit you to distribute them without approval, conditional approval, or inclusion on the Index, you cannot represent in any communications that they are safe or effective for their investigational uses. This applies to all communications

[5] Examples include Pathogenes website – tab entitled Learn More: Course 1, Course 7451, page 3; Pathogenes Website – Tab entitled Learn More: Course 1, Course 7451 page 90; and, Slideshare net; EPM 2012 updated, Slides 23, 32.

or statements made about the product, including but not limited to the Pathogenes continuing education courses you promote on your website.

3. You commercially distributed or test-marketed a new animal drug before a new animal drug application was approved pursuant to section 512(c) of the FD&C Act (21 CFR § 511.1(b)(8)(v)).

   Specifically, you provided to veterinarians investigational new animal drugs Orogin or NeuroQuel or both at a cost of up to $265.00 for the treatment of EPM. When asked by FDA investigators, you characterized this as a charge for consulting services. However, your "Shipping Information" logs include check boxes to indicate whether in connection with the shipment the client or veterinarian was billed, an invoice generated, and a credit card on file charged. These logs demonstrate that your distribution of your drugs included the intent to receive payment, and the receipt of payment.

   We note that your website at www.pathogenes.com had displayed as recently as October 2016 charges of "$200/ea" for Orogin and, "$60/ea" for NeuroQuel. In addition, your webpage describing "Field Study Enrollment Options" included the following:

   - "Orogin is for the treatment of EPM.
   - Cost is $200 per 10-day treatment, plus $8 shipping.
   - NeuroQuel is for the treatment of residual or recurrent signs of EPM post treatment.
   - Cost is $60 per 14-day treatment, plus $8 shipping.
   - You will need to pay for two screening tests and two veterinary examinations. Some animal insurance companies will pay for the testing/treatment — ask your insurance company for this information."

   This also demonstrates your practice of charging in connection with providing unapproved drugs.

   Further, CVM has made it clear that you may not charge for investigational animal drugs. On April 11, 2012 and January 30, 2013, you submitted letters requesting permission to charge fees for Orogin. While FDA sometimes in appropriate circumstances permits sponsors to recoup costs associated with investigational drug products, CVM denied those requests in letters dated July 18, 2012, and May 10, 2013. Those letters explained the reasons for CVM's denial. Despite CVM denying permission for you to recoup costs for these products, you subsequently charged veterinarians and horse owners to receive these drugs.

   We acknowledge that the current version of your website does not state prices for these drugs. However, it is not clear whether you have ceased charging for unapproved investigational drugs under the pretense of providing a consulting service.

4. You unduly prolonged distribution of a new animal drug for investigational use (21 CFR § 511.1(b)(8)(iii)).

   Specifically, approximately 585 horses were treated with the investigational new animal drugs Orogin or NeuroQuel or both during the period from January 2013 through March 2016 outside of any protocol for an adequate and well-controlled study for the treatment of EPM that could be used to support approval of these products. Further, all of these 585 horses that received your drugs and that were not under the conduct of a legitimate study must be excluded from any future study that could support either conditional approval or full approval of the products, which may further delay the investigational period by making recruitment of study subjects for a minor use even more difficult.

5. You distributed investigational articles in violation of the label requirements for distributing investigational articles (21 CFR § 511.1(b)(1)).

   Specifically, during the (b) (4) inspection, we found that neither your labels nor labeling are in compliance with the regulations because they do not bear the statements required by 511.1(b)(1). Under 511.1(b)(1) if the required statements cannot fit on the label, they may be included on the carton label and other labeling on or within the package from which the new animal drug is dispensed. The FDA investigators did not see, nor did your firm provide, any carton label or other labeling for the investigational articles that included the required statements.

IV. FAILURE TO PROVIDE AN ADEQUATE RESPONSE

Your (b) (4) response letter to the observations listed on the Form FDA 483 is inadequate and reveals a misunderstanding or lack of knowledge of the laws and regulations that a sponsor must follow when conducting clinical tests of investigational new animal drugs.

A. Notice of Claimed Investigational Exemption for a New Animal Drug

For your failure to submit NCIEs, you provided a variety of rationales including: lack of final formulations for NeuroQuel and Orogin; manufacture of these animal drugs by a third party; and, lack of approved protocols for your studies of these drugs. The regulations however contain no relevant provisions that support your rationales for failing to submit NCIEs. Your additional rationale that the components of these drugs are OTC products is likewise irrelevant; i.e., you did not distribute the approved OTC finished products but rather your own unapproved finished products containing the same active pharmaceutical ingredients as the approved products.

As noted, your lengthy submission following the inspection included pages apparently intended to represent NCIEs. These pages were vague and lacked all of the required

information, demonstrating your lack of understanding of the regulations despite communications from FDA explaining to you the requirements.[6]

B. Investigational New Animal Drug – Decoquinate Pellet

In response to the observation that you distributed decoquinate pellet without an INAD, you reference CVM's statement that to support approval for Orogin (your combination tablet product) you must demonstrate the benefit of each active ingredient. Orogin is intended for treatment of EPM. The decoquinate pellet is intended for prophylaxis of EPM according to the protocol associated with the decoquinate pellet. The intended uses are for different indications and for that reason require different study designs. Your response therefore cannot justify your distribution of this medicated feed without an INAD.

Your response also references your need for data to clarify the population intended for treatment with your investigational drugs, disagreements with CVM about appropriate testing to define the population of horses with EPM, and new information about *Sarcocystis* spp. other than S. *neurona* that cause neuromuscular disease in horses. These concerns, however, do not justify your failure to comply with the requirement for establishing an INAD when distributing a medicated feed with an intended use that does not conform to the approved labeling for the drug it contains.

C. Investigational New Animal Drugs – Claims of Effectiveness

In response to the observation that your investigational drugs were represented as effective, you elaborated on your EPM Survival Guide. You state that you needed this Guide for consulting and continuing education services to help veterinarians and horse owners understand your approach to EPM and neuromuscular diseases in horses. You state that telephone conversations alone would not suffice.

Your response suggests that you misunderstand the requirements of 511.1(b)(8)(iv), which state that the sponsor of an investigational new animal drug shall not "represent that the new animal drug is safe or effective for the purposes for which it is under investigation." Your statements, whether verbal or in writing, that your investigational products are effective are inconsistent with this requirement, and, therefore, your product does not qualify for the exemption that permits distribution of investigational products for clinical studies.

[6] Upon opening an INAD file, FDA sends the sponsor an acknowledgement letter explaining sponsor responsibilities; of which, the first section informs the sponsor of the NCIE requirements. The sponsor received this letter for Orogin (I-012092-A-0000-OT) on January 17, 2012, and NeuroQuel (I-012219-A-0000-OT) on November 27, 2012. Further, based on information provided in a subsequent meeting request, FDA was concerned the sponsor was shipping investigational product and not submitting NCIEs. Therefore, at a meeting on April 23, 2014 (I-012219-Z-0025-PS), FDA reminded the sponsor of this responsibility, and documented this in a Memorandum of Conference.

D. Test Marketing/Commercialization of Investigational Products

In response to the observation that you test-marketed investigational products, you offer that you have a consulting service; that you need to show benefit through studies acceptable to FDA; and, that drugs were not for treatment of EPM but rather sarcocystosis or inflammation. As noted, the evidence shows that the fees you charged were part of providing the products to veterinarians and others and not just for consulting services.

In addition, the FD&C Act prohibits drug sponsors from charging for unapproved investigational products to fund their studies except in exceptional circumstances. CVM informed you that those circumstances did not exist in your case. Regardless of the intended use, you cannot sell an investigational drug for uses for which it is not approved.

E. Unduly Prolonging Distribution of Investigational Product

In response to the observation that you unduly prolonged the distribution of an investigational product, you offer that CVM did not concur with submitted protocols until the third quarter of 2015. That does not explain or justify your distribution of these drugs without generating data that can be used to support your application.

Since contacting FDA about getting approval for your products, you repeatedly submitted documents whose purposes are unclear, but which appear to modify the product development plan and deviate from the agreed upon path for approval of these drugs. You also explain that you had issues with population sampling and inclusion criteria. You appear to be defining a disease by assessing individual case responses to unproven treatments, then using those responses to unproven treatments to then define the case population to demonstrate effectiveness. The effectiveness data needed for approval cannot be accomplished this way. All of the evidence CVM has to date suggests you are collecting "use" data with the sale of the product, and not conducting a study that could be justified as investigational use.

V. CONCLUSION

This letter is not intended to be an all-inclusive list of deficiencies associated with your marketing and interstate shipment of the unapproved drugs Orogin, NeuroQuel, and Decoquinate Pellet. You are responsible for ensuring that all of your products comply with the FD&C Act and its implementing regulations. Your failure to promptly correct the violations may result in enforcement action without further notice. Enforcement action may include seizure of violative products or an injunction against the distribution of violative products. In addition, your failure to correct these violations may jeopardize your eligibility for government programs; e.g., grants.

You should notify this office, in writing, within fifteen (15) working days of the receipt of this letter of the steps you have taken to bring your firm into compliance with the law. Your response should include only relevant documentation essential to show that

correction has been achieved. You should not submit irrelevant or superfluous information or documentation that is not responsive to our concerns about your violations of the law, or that does not address your corrective actions.

Because of your substantial and sustained noncompliance with statutory and regulatory requirements, and your apparent confusion about the process of developing animal drugs for FDA approval, you may want to consider hiring an expert in FDA regulatory affairs and new animal drug development to assist you with the development of your investigational new animal drugs.

If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the date by which the corrections will be completed. Include copies of any available documentation relevant to demonstrating that corrections have been made. Please direct your response to the U.S. Food and Drug Administration, Eric Nelson, Director, Division of Compliance, at Ph: (240) 402-5642 or E-mail: Eric.Nelson@fda.hhs.gov.

Sincerely,

Eric Nelson,
Director Compliance
Center for Veterinary Medicine

cc: Dr. Stuart Jeffrey, FDA, CVM, MUMS Grant Program