Inspections, Compliance, Enforcement, and Criminal Investigations

Elanco Animal Health 12-Sep-02

Department of Health and Human Services Public Health Service

Food and Chug Administration
Rockville, MD 20857

September 12, 2002
Certified Mail - Restricted Delivery
Return Receipt Requested

Patrick C. James, President
Elanco Animal Health
A Division of Eli Lilly and Company
Four Parkwood
500 East 96th Street, Suite 125
Indianapolis, Indiana 46240-3733

WARNING LETTER

Dear Mr. James:

Three inspections were concurrently conducted of Elanco Animal Health, located at 2001 W. Main Street, Greenfield, IN 46140 by Ms. Leigh Anne Myers from the Detroit District Office; Mr. Jorge F. Christian, Dr. Timothy C. Schell, and Dr. Brian D. Garthwaite from the Center for Veterinary Medicine (CVM) representing the Food and Drug Administration (Agency).

Two of the inspections focused on the firm?s operations as a Sponsor of approved investigational New Animal Drug Applications (INADs), and adherence to the Good Laboratory Practices (GLPs) under the Agency?s Bioresearch Monitoring (BIMO) Program. They were conducted between March 12 and March 22, 2002. These inspections documented significant deviations which resulted in the issuance of a Form FDA 483 - Inspectional Observations on March 22, 2002 to Douglas L. Feller, D.V.M., Executive Director, Research and Development, Elanco Animal Health.

The third inspection was conducted between March 12-22 and June 4, 2002. It focused on the firm?s post approval operations. This inspection also documented significant deviations which resulted in the issuance of a second Form FDA 483 - Inspectional Observations on June 4, 2002 to Douglas L. Feller, D.V.M., Executive Director, Research and Development, Elanco Animal Health.

The inspection covered the product Ractopamine hydrochloride. Paylean® is the registered name of the product for use in swine. The inspections covered, but were not limited to, the following subjects:

1. [redacted] Studies [redacted]
2. [redacted] Studies [redacted]
3. Effects of Ractopamine hydrochloride [redacted]
4. [redacted] Studies [redacted]
5. [redacted] Studies [redacted]
6. Post approval operations, focusing on the handling of unexpected adverse drug experience reports involving Paylean® and information concerning unusual failure of Paylean to exhibit its expected pharmacological activities.

We have reviewed the inspection reports along with the documents collected during the three inspections, the observations listed in both Forms FDA 483 which were presented to and discussed with Dr. Douglas L. Feller at the conclusion of the inspections, and the letter, dated April 5, 2002, from Dr. Douglas L. Feller to Ms. Joann Givens, Director of FDA?s Detroit District.

Based on our evaluation of the information provided in the aforementioned documents, we concluded that your firm has failed to comply with the Federal regulations governing the Sponsor?s responsibilities for investigational new animal drug studies, records and reports, and the current Good Manufacturing Practices (cGMPs).

The violations include, but are not limited to:

I. Failure of your responsibilities as a sponsor of clinical studies:

1. You failed to submit to the Agency a Notice of Claimed Investigation Exception (NCIE) for a New Animal Drug for shipments of Ractopamine hydrochloride. You had an active Investigational New Animal Drug exemption (INAD [redacted] established on [redacted] require that you submit for the Ractopamine hydrochloride. The regulations an NCIE for shipments of a drug being used for studies in support of an INAD [21 CFR 511.1(b)(4)].

In light of the existing INAD for the Ractopamine hydrochloride you should have been aware of the regulatory requirement that an NCIE be submitted to CVM for all shipments made under an INAD.

The following shipments are specific examples of this practice:

[redacted]

As these shipping records indicate you were aware that the product was being shipped for clinical trials under an INAD. Furthermore, if the drug was being shipped for tests in vitro and in laboratory animals, 21 CFR 511.1(a) requires the following label statement "Caution. Contains a new animal drug for investigational use in laboratory research animals or for tests in vitro. Not for use in humans."

In light of the shipping records referenced above, your response that these studies were "laboratory studies" is not accepted by the Agency.

2. You did not submit all information, in your possession, which would be pertinent to an evaluation of the safety and effectiveness of the New Animal Drug Application (NADA) 140-863 for Paylean® [21 CFR 514.l(b)(8)(iv)]. Specifically, that study [redacted] was not submitted to the NADA.

Your firm?s response to the Form FDA 483, dated April 5, 2002, acknowledges this observation and indicates that new Standard Operating Procedures (SOPS) have been put into place. Without reviewing these new SOPS it is not possible for the Center to determine if these new procedures would be adequate to prevent a re-occurrence of the observation.

3. You did not provide for current monitoring during the [redacted] Phase of studies Had current monitoring been conducted, the monitor would have observed that records were not always legible. Records were not recorded with a ballpoint as called for by the protocol required forms, such as the [redacted], SCORING INSTRUCTIONS", and some of the records therefore became smudged.

The Food Drug and Cosmetic Act requires "substantial evidence" of a new animal drug?s effectiveness. "Substantial evidence" means "one or more adequate and well-controlled studies." 21 CFR 514.4(a). An "adequate and well-controlled study" includes a protocol. 21 CFR 514.117(b). FDA relies on current monitoring to assure protocol adherence and reliability of data.

Your response indicates that your firm will institute steps to prevent conflicts between the protocol and the data collection techniques. You did not indicate specifically what steps would be taken to ensure current monitoring of studies to prevent protocol violations.

II. Failure of your responsibilities as a holder of NADAs for recording/evaluating and reporting of adverse animal drug experiences:

1. Your firm failed to submit a number of unexpected adverse drug experience reports and information concerning any unusual failure of the drug to exhibit its expected pharmacological activities to the FDA/CVM within 15 working days of initial receipt of the information [21 CFR 510.300(b)(2)(i) and (ii)].

21 CFR 510.300(b)(2)(i) and (ii) require that information of any unexpected side effect, injury, toxicity or sensitivity reaction or any unexpected incidence or severity associated thereof must be reported. Information concerning any unusual failure of the new animal drug to exhibit its expected pharmacological activities must also be reported.

Our conclusion of your failure to make required adverse drug experience reports is based on our review of the telephone records pertaining to Paylean® (Paylean Activity Reports) sorted by call category, which were provided to the FDA by mail with a cover letter dated April 3, 2002 from [redacted]. These telephone report include, but are not limited to:

Date of the Phone Call	Last Name of the Caller	Call Category
3/19/02	[redacted]	ADR
7/14/00	[redacted]	Product-Clinical
8/16/00	[redacted]	Product-Clinical
8/16/00	[redacted]	Product-Clinical
9/6/00	[redacted]	Product-Clinical
9/18/00	[redacted]	Product-Clinical

10/19/00	[redacted]	Product-Clinical
10/30/00	[redacted]	Product-Clinical
10/30/00	[redacted]	Product-Clinical
1/10/01	[redacted]	Product-Clinical
1/25/01	[redacted]	Product-Clinical
2/5/01	[redacted]	Product-Clinical
2/20/01	[redacted]	Product-Clinical
3/23/01	[redacted]	Product-Clinical
6/15/01	[redacted]	Product-Clinical
7/6/01	[redacted]	Product-Clinical
7/16/01	[redacted]	Product-Clinical
8/13/01	[redacted]	Product-Clinical
3/4/02	[redacted]	Product-Clinical

10/10/00	[redacted]	Product-Technical
7/26/01	[redacted]	Product-Technical
11/3/00	[redacted]	Sales/Returns

The list supplied by [redacted] is included with this letter as Attachment A.

III. Failure of your responsibilities under the cGMPs as a manufacturer of animal drug products:

1. Your firm failed to ensure that each employee has the training required to enable that employee to perform the assigned functions [21 CFR 211.25 (a) and (b)].

A. Review of the "Total Training History Report" (or "Linus Report") of the Employee [redacted] revealed that they failed to receive the following training courses:

a. Number [redacted] for the Lilly Procedure No. [redacted] for Elanco Animal Health Products (United States and Puerto Rico)" and

b. Number [redacted] for the Lilly Procedure No. [redacted] or Marketed Elanco Animal Health Products (United States and Puerto Rico)."

The Lilly procedures, [redacted] specifically list positions in the firm which are involve in receiving and/or processing of Veterinary Drug Experience Complaints. Therefore, individuals occupying these positions should have documented training in processing complaints. The individuals listed above held such positions at the time of the inspection, or in the recent past.

B. No documentation exists to show that employees [redacted] received training on the Elanco [redacted] Standard Operating Procedure No. [redacted] for Elanco Animal Health Personnel.

The Elanco [redacted] Standard Operating Procedure No. [redacted] Elanco Animal Health Personnel [redacted] lists [redacted] was being involved with [redacted]. The above listed individuals were in the [redacted] group and, therefore, should have had documented training in [redacted] proedures.

2. Your firm did not adhere to the written procedures developed for the handling of all complaints [21 CFR 211.198(a)].

Lilly Procedure No. [redacted] for Marketed-Elanco Animal Health Products (United States and Puerto Rico)." requires1 I reports summarizing all product complaints and adverse drug reaction reports received. No such report has been prepared for Paylean®.

The inspections also revealed protocol deviations in the conduct of study [redacted]. Your response indicated that this study was conducted by a Contract Research Organization (CRO), and that the CRO also conducted the quality assurance (QA) audits. As required by 21 CFR 514.l(b)(12)(iii), your firm submitted in your NADA a statement that all GLP studies were conducted in accordance with the regulations set out in 21 CFR 58 - GLP for Nonclinical Laboratory Studies.

GLPs require that studies "be conducted in accordance with the protocol." 21 CFR 58.130(a). The CRO did not follow the protocol for study [redacted]. The protocol calls for using a form to report protocol deviations but this form was not used. The protocol also states that [redacted] will not be involved in data collection, however, records infiate that [redacted] collected some data for this study. This protocol deviation was not authorize and documented as required by 21 CFR 58.35(b)(5).

It is your responsibility, as the sponsor, to assure the accuracy of all statements contained in the application. This includes information based on data supplied by a CRO.

The inspections also revealed a general problem with reporting of studies to the Agency. Study [redacted] was not reported to the INAD for Ractopamine Hydrochloride®, specifically to the [redacted].

During the course of the GLP inspection our representatives requested a complete and accurate list of all your GLP studies involving Paylean® (Ractopamine hydrochloride), including their current status as well as the names of the respective study monitors. In response, your firm supplied to our representatives multiple lists which differed in the names of the studies and their status. In addition, your firm could not locate or identify documents pertaining to some of the studies. This situation was somewhat confusing and created unneeded delays for our representatives. This concern was expressed by our inspectional team to your representatives at the conclusion of the inspection.

In order to assure compliance with 21 CFR 514.1(b)(8)(iv), we are requesting that you submit a new list with your response to this letter. The list should have the unique study identification, a full name of each study in sufficient detail to be able to determine the specific food safety issue addressed, start and completion dates of the study, name of the study director, and a description of the study status.

Furthermore, for any study where the status is identified as something other than "submitted to FDA", please explain why the GLP study was not submitted in accordance with the requirements of 21 CFR 514.1(b)(8)(iv). This section requires

that all pertinent information to an evaluation of the safety and efficacy of the new animal drug be submitted.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations. The specific violations noted in this letter may be symptomatic of serious underlying problems. You are responsible for investigating and determining the causes of the violations identified above and to prevent recurrence of similar violations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure and/or injunction. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

We request that you respond in writing within fifteen (15) working days of receipt of this letter and describe the corrective actions you have implemented, or are planning to implement, to prevent a recurrence of the violations noted above.

Please direct your written response and any pertinent documentation to:

Vernon D. Toelle, Ph.D., Team Leader
BIMO and Administrative Actions Team (HFV-234)
Division of Compliance
Office of Surveillance and Compliance
Center for Veterinary Medicine
7500 Standish Place, Suite E469
Rockville, MD 20855-2773

If you have any questions please feel free to contact either Dr. Vernon D. Toelle at 301-827-0312 or Mr. George A. Prager at 301-827-7791.

Enclosures as stated

Sincerely yours,

/s/

Gloria J. Dunnavan
Director
Division of Compliance (HFV-230)
Center for Veterinary Medicine
Office of Surveillance and Compliance

Date/Name	Question
ADR	
3/19/02 [redacted]	Received a message from his receptionist [redacted] fed 5 lb and not 5 oz of paylean to show pigs last night. Animals are down and shaking. Caller has not contacted client-does not know anything more. Wants Elanco to contact ? does not know [redacted] Asked about how to treat pigs with reactions.
Product ?Clinical	
7/14/00 [redacted]	[redacted] nutritionist said they had done some experiments and were finding a 10% death loss ? not recommending it to customer. Has a [redacted] product [redacted] is product name that includes Paylean at108 gm/ton and was told to feed it 1 lb to 5 lb of feed ? is this right? Has show pigs ? wants to buy product and dose it correctly.
8/16/00 [redacted]	What is it and how does it work? Please send info. Has a client that fed a pig Paylean and it developed diaffhea? Is this a possible side effect?
8/16/00 [redacted]	Producer fed a boar ? full feed; 280-300 lb boars at 18 gm/ton eating 10-12 lb day. Seeing animals with stress in their back legs ? 3-4 pens (10 total) with 3 animals effected ? could this be due to "withdrawal"

	of the Paylean from the [redacted].
9/6/00 [redacted]	Calling about a possible reaction to Paylean in 2 shows pigs owned by [redacted]. He thinks they weighted 260-280 lbs., and died from stress syndrome even though they tested negative. He said that [redacted] had talked to [redacted] about 10 days ago. [redacted] thought there should be a warning if this was a reaction to Paylean and he was concerned about recommending it use.
9/18/00 [redacted]	Caller has had pigs on Paylean for about 2-3 weeks and is showing signs of stiffness in the back legs. Want to know if he should back off the feed. Bought Paylean from [redacted] distributors. Feeding 18 gm/ton in [redacted] feed. 4/4/ on Paylean thinks it makes
10/19/00 [redacted]	Caller has some questions about breeding in show pigs after feeding Paylean. 7 gilts were on Paylean (levels unknown) for approximately 85 days (12 weeks) and have been off since 8/15. Gifts have not come into heat, have been Al bred 2 times and several are coming into heat again. Wants to know what to do, what is the outcome?
10/30/00 [redacted]	Called before ? has seen show pigs with lameness ? curious [redacted] (sales mgr). Fed some animals at 18 gm/ton study (now thinking about doing a study with 9 gm/ton) 12 on feed, 11 went to show, 4 had lameness, stiffness that they worked out of. Were fed 5 weeks before show. Do they need to go to 9 gm with same results?

	Fed in weight range-all things promised, delivered, but how can they
10/30/00 [redacted]	Customer using Paylean ? pigs "tying up" on product ? 1 boar, "goose stepping", muscles tight. Inadvertently fed boar Paylean ? 9 gm for two weeks. Animals was really heavily muscle ? also had joint problems, but vet knows this is a muscle problem.
1/10/01 [redacted]	[redacted] feeding it show pigs [redacted] feed. Spoke to [redacted]. One pig has had some "tying up" syndrome - pulled off Paylean, was had for 3 days, had tremors (a sort of withdrawal symptom?) Feeds a [redacted] program that includes non-medicated as well as medicated feed. Pig weights approx. 230lb. Very satisfied with the product in all other ways.
1/25/01 [redacted]	[redacted] has adverse reaction question - has seen [redacted] tying up like syndromes in show pigs (6 deaths/240); is concerned about vet?s role in helping those showing pigs. Wants to report this to Elanco before reporting to FDA.
2/5/01 [redacted]	Callers were [redacted] have received-e-mails (at least 2) that have been from customers using the [redacted] to feed show animals ? 1 [redacted] reports dying animals 2) Other lady - downer pigs: No specific details. [redacted] know how to handle these inquiries.
2/20/01 [redacted]	Caller was feeding Paylean and some of his pigs have developed a cough and other

	resp. problems. He wanted to know if their was a withdrawal period for Paylean before he moved the sick pigs.
3/23/01 [redacted]	Caller believe some Paylean feed may have been fed to nursery pigs. Spoke with [redacted] the pigs are very wide, heavily muscled and exhibit exhaustion easily on moving. He thinks maybe the coop did not flush the line before mixing nursery feed and there was some Paylean in it. The farm received feed on 3/3 and 3/15/01. Caller asked if Paylean could be tested for in blood.
6/15/01 [redacted]	Caller had questions on feeding Paylean at the 9 g/ton level. Feeding show animals - thinks it may have caused some "hyperactivity" in a but has seen this behavior in the pig?s dam. Received a bucket of a [redacted] product after winning reserve at a show.
7/6/01 [redacted]	Caller has a client who has a show pig that died while on Paylean. Caller?s client fed 2 pigs Paylean at 18 gm/ton - mixed it in milk replacer and fed it in 5 Ibs of feed on 6/30/01. Vet thinks there may have been heat related death - may have done post mortem, but not certain. [redacted] had worked out the calculations with the customer-feels he was feeding it correctly. Does not feel the Paylean caused deaths nor did owner-just checking the toxicity studies.
7/16/01 [redacted]	Questions about its use in show pigs - did use it last year. Has had some stiff pigs - was wondering if this is the same as a

	"downer pig" that he read about on the internet. Wondering about the possibility that certain genetics that might be too lean for the product
8/13/01 [redacted]	[redacted] customer has reported pig vomiting after eating feed with Paylean. It eats a little and then vomits. Has done this repeatedly.
3/4/02 [redacted]	Caller reports that gilts (200) shown at [redacted] livestock Show were given an ultrasound at the end of the show o determine carcass benefits. [redacted] did dx and was said to be "alarmed" by looking at the ovaries - but no details on what "alarmed" meant or who did the exam. Gilts were assumed to be fed Paylean, but no confirmation and no info on how much, how long, etc. Caller said 24 gilts were sold to producers in area -wants to know how they will respond when bred. Asked about studies, etc. Also asked if carnitine could cause problems if used in conjunction.
Product-Technical	
10/10/00 [redacted]	Caller wants to speak with some one about Paylean that his pigs did not respond well.10/18 - Fed 150 hogs in finishing started at 200 lb but is "guessing"; fed Paylean with bean meal. August 15 ? October 15 fed at what level; Measured yield and leanness ? has 51.5% lean; control barn was better. Pigs weighed the about the same; didn?t feel efficiency changed. Down a point on DelPhl (IPC) - was told IBP would have measured this

	differently on leanness. [redacted] is rep for company - Last 4 weeks thought he had it where he wanted - about 10 groups of 40
7/26/01 [redacted]	Caller started using product this winter at the 4.5 g/ton level. He believes the affects are now tapering off. Is there a problem with hot weather and the storage of Paylean? Have we heard of this before?

Sales Returns

11/3/00 [redacted]	Will the pigs "fall apart" after they have been on Paylean for about 4 weeks and then are taken off? Feeds animals for 4 weeks and has 50-100 that are kept over for 2-3 wks before going to market. What will happen to these animals? Started feeding about 10 days ago - had trouble finding product and thinks barrows were very hyper after feeding for about 3 days - fed at 9 gm/ton. Is thinking about reducing the dose to 4.5 gm/ton.