

This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

See reverse side for additional information.

Interagency Report Control No 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. REGISTRATION NO. 93-R-0280 CUSTOMER NO. 1117

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

2. HEADQUARTERS RESEARCH FACILITY (Name and Address, as registered with USDA, include Zip Code)

ELAN PHARMACEUTICALS, INC. "A" by
800 GATEWAY BLVD.
SAN FRANCISCO, CA 94080 R. Doherty

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

FACILITY LOCATIONS (sites)

ELAN PHARMACEUTICALS, INC.
SAN FRANCISCO, CA 94080

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01/19/06

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS FORM 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs			597	626	1223
7. Hamsters					
8. Rabbits					
9. Non-Human Primates					
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

- 1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.
- 2) Each principal investigator has considered alternatives to painful procedures.
- 3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). A summary of all the exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.
- 4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional official)
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143)

SIGNATURE OF C.E.O. OR INSTITUTIONAL OFFICIAL

NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (Type or Print)

DATE SIGNED

(B)(6) (B)(7)(c)

11/03/2005

1. Registration Number: 93-R-0280 / 1117

2/3. Species (common name) & Number of animals used in this study:

Guinea Pigs (626)

4. Explain the procedure producing pain and/or distress.

Young adult or juvenile guinea pigs are weighed, numbered, and shaved at the injection site (nuchal area approximately 8cm in length) and wiped with betadine or alcohol swab. Each guinea pig is immunized by 5 intradermal injections of 120ul in shaved area with the immunogen emulsion. Sores will appear at immunization site, animals will be treated with benzalkonium chloride derivative or chlorhexidine disinfectant to be sprayed, or iodine derivative topical ointment on the affected area. Once scab formation is observed at the injection site, sore treatment will be discontinued, however the area will be monitored and retreated if necessary. The immunized animals are expected to develop hind limb paralysis approximately 10-17 days post immunization, and will be checked daily. If a guinea pig? Food will be placed in closer proximity to the bottom of the cage in an open container for greater accessibility, to allow ad libitum consumption by guinea pigs that have motor impairment that might prevent them from feeding from fixed feed bins. Water b In addition to the post immunization care stated above, some guinea pigs may require extra care. Typically, these pigs will have partial or complete hind limb paralysis (clinical score of 2.5 or above) that makes it more difficult for them to reach their Guinea pigs who have been identified with hind-limb paralysis will have their hind-limbs and feet inspected to ensure no chewing of appendages has occurred. If chewing is noted, the leg or affected area will be rinsed with tap water and chlorhexidine disinfectant, or iodine ointment. Once the leg is dried, a bandage such as either a band-aid, a 3x3 gauze pad wrapped in Parafilm, Vetwrap, or dental dam will be adhered to the area to deter further chewing. To further secure the wrap, a piece of white tape may be attached, if deemed necessary. Caution will be taken in unwrapping the bandage to prevent abrasions. Bandages will be replaced daily since infections can set in quickly. If an infection develops or leg is badly damaged, the animal is to be euthanized. In order to provide symptomatic relief of disease related pain and distress, animals will be monitored regularly and provided appropriate care as listed in table 1. All care will be recorded on the animal?

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

The guinea pigs may experience some pain after the immunization. During the paralysis, the guinea pigs do not appear to experience acute or surgical type pain. They are active and do not show behavior typical of guinea pigs in pain, but they likely exper

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

Agency:

CFR:

Approval Status:

Approved/Disapproved By:

Date:

Disapproved Reason:

APHIS Form 7023 Column E Explanation

This form is intended as an aid to completing the APHIS Form 7023 Column E explanation. It is not an official form and its use is voluntary. Names, addresses, protocols, veterinary care programs, and the like, are not required as part of an explanation. A Column E explanation must be written so as to be understood by lay persons as well as scientists.

1. Registration Number: 93-R-0280

2/3. Species (common name) & Number of animals used in this study:

Guinea Pigs (626)

4. Explain the procedure producing pain and/or distress.

Young adult or juvenile guinea pigs are weighed, numbered, and shaved at the injection site (nuchal area approximately 8cm in length) and wiped with betadine or alcohol swab. Each guinea pig is immunized by 5 intradermal injections of 120ul in shaved area with the immunogen emulsion. Sores will appear at immunization site, animals will be treated with benzalkonium chloride derivative or chlorhexidine disinfectant to be sprayed, or iodine derivative topical ointment on the affected area. Once scab formation is observed at the injection site, sore treatment will be discontinued, however the area will be monitored and retreated if necessary.

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results. (For Federally mandated testing, see Item 6 below)

The guinea pigs may experience some pain after the immunization. During the paralysis, the guinea pigs do not appear to experience acute or surgical type pain. They are active and do not show behavior typical of guinea pigs in pain, but they likely experience symptomatic distress resulting from the disease. The disease can cause dehydration, atonic bladder, fecal impaction and weight loss. Continuous administration of pain ameliorating drugs will interfere with the results of experiment and is not likely to relieve the pain or distress related to these symptoms. These symptoms are each addressed individually in the post immunization care section of this protocol and in Table 1. We hope that our treatments will prevent the paralysis and the distress, so that only 30% of the guinea pigs (the negative control group) in a study may experience the temporary paralysis.

6. What, if any, federal regulations require this procedure? Cite the agency, the code of Federal Regulations (CFR) title number and the specific section number (e.g., APHIS, 9 CFR 113.102):

Agency:

CFR:



800 Gateway Boulevard
South San Francisco, CA 94080
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Kathy Garland, DVM
Supervisory Animal Care Specialist
Western Region, Animal Care

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Dear Dr. Garland:

We are sending the additional information for our facility's annual report (APHIS Form 7023) requested in your letter dated December 7, 2005.

Regarding your request for clarification to item #4 and #5 and additional information as indicated below.

1. Please clarify the 6th sentence which begins "If a guinea pig? Food will be placed...fixed feed bins."

Reply: If a guinea pig's clinical score progresses to greater than or equal to 3.5 (complete hind-limb paralysis, some forelimb paralysis), they will then be checked by an investigator every 12 hours, and any necessary care will be provided (e.g. supplemental hydration, bandaging, etc as described below). Food will be placed in closer proximity to the bottom of the cage in an open container for greater accessibility, to allow ad libitum consumption by guinea pigs that have motor impairment that might prevent them from feeding from fixed feed bins.

2. Please clarify the 7th sentence which begins "Water b In addition...require extra care."

Reply: Water bottles will be fashioned with longer sipper tubes to allow greater accessibility. Subcutaneous fluids (0.9% saline or Lactated Ringers Solution, 3-10ml per guinea pig per day) may be supplied if necessary, as determined by testing the elasticity and pliability of the skin by pinching a fold of skin between one's fingers. In addition to the post immunization care listed in the table, some guinea pigs may require extra care.

3. Please clarify the 8th sentence which has the incomplete ending "...difficult for them to reach their Guinea pigs..."

Reply: Typically, these pigs will have partial or complete hind limb paralysis (clinical score of 2.5 or above) that makes it more difficult for them to reach their

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food and water. These pigs will often eat and drink if removed from their cage bedding and given ready access to food and water on a sturdy surface. These animals may be placed in an inverted cage lid or suitable tray that has been layered with an absorbent pad. Up to three guinea pigs may be placed in one cage lid. A plastic multi-feeding station may also be used, with only one guinea pig allowed per individual pen. For each guinea pig, there should be a water bottle positioned with its sipper tube extending over the lip of the cage lid, tray, or multi-feeding station so that it is at the height of the pig's head. Food pellets should also be placed in the inverted lid for easy access. These guinea pigs may be placed in the cage lid, tray, or multi-feeding station in the morning (after the daily monitoring) and may remain there until the end of the workday (8 hours maximum). At the end of the workday, these guinea pigs will be checked for hydration before being put back in their cages and, if needed, they will be given s.c. ringers or saline. The need for extra care will be determined daily by a project associate when each animal is weighed and assigned a clinical score. If determined, these paralyzed guinea pigs will also be given vitamin C or multi-vitamin tablets to supplement nutrients present in guinea pig chow, but not in nutripet or nutritional supplement. Guinea pigs who have been identified with hind-limb paralysis will have their hind-limbs and feet inspected to ensure no chewing of appendages has occurred.

4. The referenced "table 1", is not included with the explanation. Please provide this table.

Reply: **Clinical Scoring Parameters (Table 1)**

EAE GRADE	CLINICAL SIGNS	INTERVENTION ACTION
0	No abnormality	Baseline weight
1	Abnormal gait. Pig may "wobble" or lean to one side as it walks. Partial paralysis of one leg may also be present. A pinched waist is often noticed especially at the hind limbs	Initiate a medical record. Initiate an EAE chart and record weight(s). Animal care is provided as needed for the following 1.) Dehydration – Animals will be offered water from the sipper tube and given s.c. lactated Ringers solution or saline (3-10ml). To be performed daily after score of 2 is reached 2.) Atonic bladder – Bladders will be expressed manually if urinary incontinence is present. 3.) Fecal Impaction – Laxative such as Tonic-Lax will be administered to individual pigs experiencing constipation as needed.

		4.) Weight Loss – Animals under 250grams should receive nutrient supplement (Nutripet or Nutrical) daily. Nutrient supplement can be placed in a dish in the cage or be force fed via syringe
2	<p>Bi-lateral hind limb weakness. Animal is unable to support its hind limbs consistently. Inability to right itself when placed on its back and held in hand</p> <p>A clinical score of 2.5 may be given to animal which is unable to support its hind limbs, and no longer uses them for mobility. However, animal is not completely paralyzed in the hind limbs.</p>	<p>In addition to care listed above, animals should be placed in their own cage or housed with another pig with a score of “2”.</p> <p>Assure proper hydration daily.</p> <p>Make sure food is available in clean containers set on the floor of the cage. Clean, disinfect and bandage hind limbs if animal has been chewing toes or feet. Animals with impaired mobility should also have anal region cleaned by benzalkonium chloride derivative disinfectant to prevent infection.</p> <p>Same care criteria as for a clinical score of 2.</p>
3	<p>Complete hind limb paralysis. Animal is unable to move hind limbs, motility limited to fore limbs only.</p> <p>A clinical score of 3.5 may be given to an animal that displays some fore limb weakness or mild paralysis, or is unable to remain upright to eat/drink..</p>	<p>Same care criteria as for a clinical score of 2.</p> <p>An animal with a clinical score of 3.5 is deemed “critical” and will be monitored every (12) twelve hours. If score remains at 3.5 for (24) twenty-four hours then the animal requires euthanization.</p>
4	<p>Moribund, ie. the animal is unable to right itself for locomotion, or complete paralysis of all limbs.</p>	Euthanize

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5. Please provide justification as to how administration of an analgesic that does not provide anti-inflammatory properties, such as oral administration of acetaminophen, would adversely affect the experiment.

Reply: Analgesics that reduce inflammation would directly interfere with the evolution and progression of EAE in guinea pigs and therefore cannot be used, due to the inflammatory nature of this disease. Although acetaminophen has not been reported to have significant effects upon inflammation, it may have other untoward effects that would invalidate our compound efficacy studies.

Metabolism of drug candidates in animals is an important factor in determining pharmacokinetic properties, efficacy and potential toxicity of our compounds. Treatment with acetaminophen is likely to alter pharmacokinetic properties, especially those attributed to liver function. This has the potential to adversely effect compound efficacy and may also result in unexpected toxicity.

If you have any questions, feel free to contact me at (b)(6), (b)(7)c

Sincerely,

(B)(6) (B)(7)(c)

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