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 21!

See attached form for additional information.

Interagency Report Control No.:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

# ANNUAL REPORT OF RESEARCH FACILITY

( TYPE OR PRINT )

1. **CERTIFICATE NUMBER:** 93-R-0067
**CUSTOMER NUMBER:** 1168

FORM APPROVED
OMB NO. 0579-0036

Allergan
P.O. Box 19534
Irvine, CA 92623

Telephone: (714) -246-2606

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

FACILITY LOCATIONS ( Sites ) - See Atached Listing

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

| A. Animals Covered By The Animal Welfare Regulations | B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes. | C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o 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 an 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 wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. ( An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report | F. TOTAL NUMBER OF ANIMALS ( COLUMNS C + D + E ) |
|---|---|---|---|---|---|
| 4. Dogs | | 9 | 27 | 4 | 40 |
| 5. Cats | | 10 | - 0 - | - 0 - | 10 |
| 6. Guinea Pigs | | 2 | 60 | - 0 - | 62 |
| 7. Hamsters | | - 0 - | - 0 - | - 0 - | - 0 - |
| 8. Rabbits | | 689 | 2213 | 7 | 2909 |
| 9. Non-human Primates | 31 | 15 | 169 | 3 | 187 |
| 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 anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese 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 ap Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary inc 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 )

NOV 18 2008

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

DATE SIGNED 11/13/08

APHIS FORM 7023 (Replaces VS FORM 18-2[illegible] (OCT 88), which is obsolete.)
( AUG 91 )

## Column E Explanation

This form is intended as an aid to completing the 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-0067

2. Number 4 of animals used in this study.

3. Species (common name) DOG of animals used in the study.

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

The procedure for this study was the oral or parenteral administration of a candidate therapeutic agent to dogs with the purpose of evaluating the potential toxicity of this therapeutic agent. The test agents were given daily by oral gavage or capsule, subcutaneous or intravenous injection. Doses were selected so as to produce some toxic effect at the higher dose range. The study was done to fulfill regulatory requirements for non-rodent safety evaluation for prediction of the safety of the agent for humans.

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)

Toxicology data is required by drug regulatory agencies to determine if new test agents are safe for administration into humans. Dosages are selected to minimize mortality, moribundity, pain and/or discomfort. Most animals will receive no pain or discomfort from the treatment, but it is possible that some animals treated with the high dose may show symptoms such as lethargy, sedation, decreased motor activity, abnormal gait, dehydration, rough hair coat, and/or diarrhea. Other adverse symptoms are also possible. The four animals on this study developed emesis followed by mild to moderate seizure activity.

Analgesics cannot be given to alleviate potential pain/discomfort because sedation or anti-inflammatory effects or other drug related issues have the potential to interfere with determination of the toxic endpoint, determination of the target organ, or confound determination of reversibility from toxicity. In addition, toxic effects may make the animals ill but not necessarily in pain so use of analgesics or anesthetics may not be of benefit to the animals anyway and could potentially make them worse. Nursing care was provided to these four animals after development of emesis and they were euthanized after the onset of seizures.

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_____

## Column E Explanation

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1. Registration Number: 93-R-0067

2. Number 7 of animals used in this study.

3. Species (common name) Rabbit of animals used in the study.

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

The procedure for this study involves the administration of a (b)(4) into the vitreous of the eye unilaterally in an animal (b)(4) in order to produce a model fo (b)(4) In general the inflammation is mild to moderate and the animals appear to tolerate the condition quite well. They continue to eat and drink normally and display normal behavior. In the early stage of model development some of the early dose response testing resulting in (b)(4) and the animals appeared uncomfortable. Dose selection was adjusted to refine the model.

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)

This is a model to induce (b)(4) is commonly associated with pain and discomfort so by design the animal may be in some pain or discomfort. The purpose of the study is to evaluate new test compounds that will limit or alleviate (b)(4) or discomfort so for most of the animals on study the discomfort is minimal. The control animals however by necessity of the scientific study cannot receive any (b)(4) treatment. Animals that were noted to have [redacted] were treated with buprenorphine daily and supplemented with vegetables for a few days while [redacted] and clinical signs associated with pain subsided, or euthanized if the problem did not subside. Buprenorphine has been demonstrated to have some (b)(4) activities (Volker,D., Bate,M., Gentle,R., and Garg,M., Oral buprenorphine is (b)(4) and modulates the pathogenesis of (b)(4) in the Lew/SSN rat, Lab Anim, 34 (2000) 423-429) so the chronic use of this drug for pain or discomfort would be incompatible with the scientific mission of this study. Chronic use of opioids for pain management is also thought to have effects upon appetite and body weight maintenance. For the animals with mild to moderate (b)(4) with no apparent clinical signs it was decided that it would not be prudent or scientifically sound to treat these animals using opioids.

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 _____

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1. Registration Number: 93-R-0067

2. Number 3 of animals used in this study.

3. Species (common name) CYNOMOLGUS of animals used in the study.

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

**The procedure for this study was a single intramuscular administration of (b)(4) or a related compound under development). At higher doses (b)(4) may cause mild to severe systemic signs of toxicity over a period of days. Mild clinical signs include ptosis, and mild ataxia. Moderate clinical signs include an increase in ataxia, and decrease to loss of appetite and occasional open mouth breathing. Severe clinical signs would be lateral recumbancy and labored breathing. If clinical signs develop it will typically be within 10 days. Clinical signs may progress from mild to severe or not progress and resolve within 5-10 days.**

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 scientific need was a pilot study to evaluate the relative safety of a new developmental molecule compared t (b)(4) in a non-rodent species so decisions could be made by upper management regarding further development of these new compounds. There is no pain associated with (b)(4) ut as symptoms develop the animal could be in distress. Animals that show signs of toxicity were treated symptomatically with appropriate veterinary care to alleviate or minimize distress. Animals were euthanized immediately if clinical conditions progressed from moderate to severe. The use of analgesics or anesthetics for the relief of pain is not warranted because there is no "pain" associated with this model. The use of these agents could actually be detrimental and further compromise the animals' ability to eat, drink and maintain normal functions.**

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_____

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