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OMB APPROVED
0579-0036

This report is required by law (7 U.S.C. 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.

Interagency Report Control No. 0180-DOA-AN

Fiscal Year: 2009

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

REGISTRATION NUMBER: 31-R-0021

Customer Number: 228

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

Battelle Memorial Institute
505 King Avenue
Columbus, OH 43201

Telephone: (614) 424 7444

NOV 27 2009

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)* *See Attached Listing*

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 on these animals and the reasons such drugs were not used must be attached to this report.)*	F. TOTAL NUMBER OF ANIMALS **(Cols. C + D + E)**
4. Dogs		485	52	4	541
5. Cats					
6. Guinea Pigs	346	1,952	320	1,369	3,641
7. Hamsters		250		102	352
8. Rabbits		453	145	295	893
9. Non-human Primates	173	809	360	424	1,593
10. Sheep					
11. Pigs		14	140		154
12. Other Farm Animals					
13. Other Animals					
Ferrets		266		74	340

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 such 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 provisions 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 (C.E.O.) or Legally Responsible Institutional Official (I.O.))
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

(b)(6), (b)(7)c

DATE SIGNED 11-24-09

AUG 2009

EG 12-4-09

Summary of Exceptions to the Regulations or Standards

Note: Exceptions were IACUC-reviewed and approved.

A. Sanitization of Primary Enclosures

1. Variances were granted to the cage change requirement.

   a. This variance was granted to avoid interference with cardiovascular data collection and requirements for specialized caging. The cages were cleaned twice daily as per standard procedure.
      i. Species: Primate
      ii. Number: 48
   b. This variance was granted due to corridor maintenance work including floor painting. The cages were cleaned twice daily as per standard procedure.
      i. Species: Dog
      ii. Number: 8
   c. This variance was granted to minimize handling of animals being transferred offsite. The cages were cleaned twice daily as per standard procedure.
      i. Species: Primate
      ii. Number: 20
   d. This variance was granted to avoid repeated anesthesia events by combining activities. The cages were cleaned twice daily as per standard procedure.
      i. Species: Primate
      ii. Number: 8
   e. This variance was granted due to study requirements. Room temperature measurements were critical to this study (temperature effects on cardiovascular parameters were being studied) and opening the room doors for a prolonged time for cage change could confound results. The cages were cleaned twice daily as per standard procedure.
      i. Species: Primate
      ii. Number: 20
   f. This variance was granted to minimize handling and allow randomization and transfer by combining activities. The cages were cleaned twice daily as per standard procedure.
      i. Species: Primate
      ii. Number: 44

B. Cage Size

1. Exceptions were made to the cage size requirement.

   a. Due to telemetry data collection requirements, the animals were housed in a single cage for ~12 hours prior to each dosing through ~48-96 hours following each dosing for a total of 4 dosing days with ~7-10 days of rest between each dosing.
      i. Species: Dog
      ii. Number: 2

b. This exemption was made to allow the collection of cardiovascular data. Cages were cleaned at least every other day and the animals could express normal postural adjustments, had ready access to food, water and clean bedding. Additionally a variance to the relative humidity was approved.
   i. Species: Guinea pig
   ii. Number: 4

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 41

3. Species (common name) of animals used in this study: Ferret

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

   Intramuscular injection. The dosing procedure involved an injection with a proprietary vaccine which did not cause more than momentary pain or distress. The administration of infectious material via intranasal instillation was carried out under anesthesia, and did not cause any distress, however the resultant viral infection may have caused pain and/or distress.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to determine the efficacy of a proprietary vaccine and provide proof of concept for the development of an anti-viral prophylactic [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 30

3. Species (common name) of animals used in this study: Ferret

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

   Intramuscular injection. The dosing procedure involved oral administration of a therapeutic agent which did not cause more than momentary pain or distress. The administration of infectious material via intranasal instillation was carried out under anesthesia, and did not cause any distress, however the resultant viral infection may have caused pain and/or distress.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications

could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   N/A

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 3

3. Species (common name) of animals used in this study: Ferret

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

   The administration of infectious material via intranasal instillation was carried out under anesthesia, and did not cause any distress; however the resultant viral infection may have caused pain and/or distress. Subsets of animals were previously vaccinated.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used since the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals did exhibit signs of infection including cough, sneezing and low grade fever, however the activity scores remained at 0 and 1 throughout the experiment. No animals required euthanasia during this study.

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:

   This work was conducted to determine the efficacy of a proprietary vaccine against challenge with 2009 H1N1 influenza and provide proof of concept for the development of an anti-viral prophylactic [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 44

3. Species (common name) of animals used in this study: Guinea Pig

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

   Neurotoxin administration. The dosing procedure involved an intramuscular injection which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress. This work was conducted in support of future studies to evaluate the efficacy of therapeutic and post exposure prophylaxis.

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.

   Anesthetics, analgesics and sedatives may have masked and/or potentiated the effects of botulinum intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were terminated to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   This work was conducted develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 124

3. Species (common name) of animals used in this study: Guinea Pig

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

   Neurotoxin and anti-serum administration. The dosing procedure involved an intramuscular and intraperitoneal injection which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress. This work was conducted in support of future studies to evaluate the efficacy of therapeutic prophylaxis.

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:

   Anesthetics, analgesics and sedatives may have masked and/or potentiated the effects of botulinum intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were terminated to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

This work was conducted develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 398

3. Species (common name) of animals used in this study: Guinea Pig

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

   Intradermal injection. The dosing procedure involved an injection with bacterial spores which did not cause more than momentary pain or distress. The resultant bacterial infection may have caused pain and/or distress.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 204

3. Species (common name) of animals used in this study: Guinea Pig

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

   The guinea pigs were subjected to an intramuscular and subcutaneous injection. The intramuscular treatment injections and the subcutaneous challenge dosing procedure did not cause more than momentary pain or distress. Seizure activity, if present, may have caused pain and/or distress.

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.

   To estimate the physiological effects in man, guinea pigs were exposed to compounds. It is necessary to use a species of animal known to respond to compounds in a manner similar to that of man. There are no known

characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered without signs of pain and those with severe signs died rapidly.

Anesthetics, analgesics and tranquilizers would have interfered with the physiological effects of this compound. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. These data are critical to human safety in the event of exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 254

3. Species (common name) of animals used in this study: Guinea Pig

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

   Neurotoxin administration. The dosing procedure involved an intramuscular injection which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress. This work was conducted to evaluate the efficacy of therapeutic and post exposure prophylaxis.

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.

   Anesthetics, analgesics and sedatives may have masked and/or potentiated the effects of botulinum intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 62

3. Species (common name) of animals used in this study: Guinea Pig

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

   The guinea pigs were subjected to topical application of an agent. The application procedure did not cause more than momentary pain or distress. Seizure activity, if present, may have caused discomfort and/or pain or distress. This work was conducted to evaluate the effectiveness of a decontamination system.

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.

   To estimate the physiological effects in man, guinea pigs were exposed to compounds. It is necessary to use a species of animal known to respond to compounds in a manner similar to that of man. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered without signs of pain and those with severe signs died rapidly.

   Anesthetics, analgesics and tranquilizers would have interfered with the physiological effects of this compound. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. These data are critical to human safety in the event of exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 96

3. Species (common name) of animals used in this study: Guinea pigs

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

   The challenge was performed via inhalation. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of monoclonal antibodies, antibiotic treatment and/or vaccination.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting

euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   N/A

Column E Explanation Form

1. Registration Number:

2. Number of animals used: 50

3. Species (common name) of animals used in this study: Guinea Pig

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

   Neurotoxin administration. The dosing procedure involved an intramuscular injection which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress.

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.

   Anesthetics, analgesics and sedatives may have masked and/or potentiated the effects of botulinum intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 35

3. Species (common name) of animals used in this study: Guinea Pig

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

   Oral gavage administration of toxins. The dosing procedure did not cause more than momentary pain or distress. The resultant toxicity may cause pain and/or distress.

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.

Anesthetics, analgesics and sedatives may potentate the effects of intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs are not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs that met the criteria for euthanasia established in the protocol or those which were moribund were euthanized to alleviate pain and distress. This data is critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 38

3. Species (common name) of animals used in this study: Guinea Pig

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

   Neurotoxin administration. The dosing procedure involved an intramuscular injection which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress. This work was conducted to evaluate the efficacy of therapeutic and post-exposure prophylaxis.

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.

   Anesthetics, analgesics and sedatives may have masked and/or potentiated the effects of botulinum intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 64

3. Species (common name) of animals used in this study: Guinea Pig

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

   Neurotoxin administration. The dosing procedure involved an intramuscular injection which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress. This work was conducted to evaluate the efficacy of therapeutic and post exposure prophylaxis.

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.

   Anesthetics, analgesics and sedatives may have masked and/or potentiated the effects of botulinum intoxication and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 182

3. Species (common name) of animals used in this study: New Zealand White Rabbit

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

   Aerosol challenge with bacterial spores. The challenge was performed using a muzzle-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of monoclonal antibodies, antibiotic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which

were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 29

3. Species (common name) of animals used in this study: New Zealand White Rabbit

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

   Aerosol challenge with bacterial spores. The challenge was performed using a muzzle-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of monoclonal antibodies, antibiotic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   N/A

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 49

3. Species (common name) of animals used in this study: New Zealand White Rabbit

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

   Aerosol challenge with bacterial spores. The challenge was performed using a muzzle-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of monoclonal antibodies, antibiotic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 8

3. Species (common name) of animals used in this study: New Zealand White Rabbit

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

   Aerosol challenge with bacterial spores. The challenge was performed using a muzzle-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   N/A

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 16

3. Species (common name) of animals used in this study: New Zealand White Rabbit

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

   Aerosol challenge with bacterial spores. The challenge was performed using a muzzle-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of monoclonal antibodies, antibiotic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 11

3. Species (common name) of animals used in this study: New Zealand White Rabbit

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

   Aerosol challenge with bacterial spores. The challenge was performed using a muzzle-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress.

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.

Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   N/A

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 83

3. Species (common name) of animals used in this study: Syrian Golden Hamsters

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

   Subcutaneous injection of virus. The injection did not cause more than momentary pain or distress, however the resultant viral infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness and window of treatment of monoclonal antibodies for therapy.

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.

   Anesthetics, analgesics, and sedatives could not be provided because they had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that the use of pain medications could mask the clinical appearance, affecting the experimental data. Supportive care in the form of a hydration supplement was provided. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 19

3. Species (common name) of animals used in this study: Syrian Golden Hamsters

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

   Intraperitoneal injection of virus. The injection did not cause more than momentary pain or distress, however the resultant viral infection may have caused pain and/or distress. This work was also conducted to evaluate the effectiveness of a therapeutic.

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.

   Anesthetics, analgesics and sedatives may potentiate the effects of infection and could confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to determine the efficacy of a therapeutic and provide proof of concept for the development of an anti-viral prophylactic [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 165

3. Species (common name) of animals used in this study: Cynomolgus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals: 18

3. Species (common name) of animals used in this study: Cynomolgus macaque

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

   Aerosol challenge. The challenge was performed in non-anesthetized animals by inhalation using a head-only exposure chamber. The challenge procedure itself is not painful but effects of the agent may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment (proprietary) on post-exposure neurobehavior using testing panels. The test panel rewarded animals for successful test taking behavior measured by animals responding to tasks on a computer touch sensitive screen and was not painful or stressful.

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.

   Anesthetics, analgesics, and sedatives could not be provided because they had the potential to mask or potentiate the effects of the agent. There are no known characterized, surrogate markers to predict effects on neurobehavioral functions following these types of exposures. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals: 163

3. Species (common name) of animals used in this study: Cynomolgus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may

have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 11

3. Species (common name) of animals used in this study: Cynomolgus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress.

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 15

3. Species (common name) of animals used in this study: Cynomolgus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 10

3. Species (common name) of animals used in this study: African green monkey

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the natural course of the disease and identify treatment endpoints for subsequent studies.

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 11

3. Species (common name) of animals used in this study: African green monkey

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I--approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of

effectiveness from studies in animals (under subpart H--approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 9

3. Species (common name) of animals used in this study: Rhesus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 7

3. Species (common name) of animals used in this study: Rhesus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of infection and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 4

3. Species (common name) of animals used in this study: Rhesus macaque

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

   Aerosol challenge with neurotoxin. The challenge was performed under Telazol® anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant intoxication may have caused pain and/or distress. This work was conducted to evaluate the effectiveness of a therapeutic treatment and/or vaccination (proprietary).

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.

   Anesthetics, analgesics, and sedatives could not be provided because it had the potential to mask or potentiate the effects of the neurotoxin and confound results. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. Pain-relieving drugs were not used, on the basis that death is rapid following the onset of symptoms, and that the use of pain medications could mask the clinical appearance, affecting the experimental data. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress. These data are critical to human safety in the event of human exposure.

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:

   This work was conducted to qualify a model and develop data necessary for definitive studies [required by the federal government under 21CFR314.610 - subpart I -approval of new drugs when human efficacy studies are not ethical or feasible, and/or 21CFR601.91 - subpart H -approval of biological products when human efficacy studies are not ethical or feasible].

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 11

3. Species (common name) of animals used in this study: Rhesus macaque

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

   The animals were subjected to an intramuscular injection. The intramuscular treatment injections and the intramuscular challenge dosing procedure did not cause more than momentary pain or distress. Seizure activity, if present, may have caused pain and/or distress.

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.

   To estimate the physiological effects in man, the monkeys were exposed to compounds. It is necessary to use a species of animal known to respond to compounds in a manner similar to that of man. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild to severe clinical signs generally recovered without signs of pain after treatment. The few animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were found to be moribund were euthanized to alleviate pain and distress.

   Anesthetics, analgesics and tranquilizers would have interfered with the physiological effects of this compound. Experienced staff veterinarians and animal technicians were on site to monitor the study conduct and any animal welfare issues. These data are critical to human safety in the event of exposure.

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:

   Agency: FDA

   CFR: As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR314.610, approval based on evidence of effectiveness from studies in animals (under subpart I -approval of new drugs when human efficacy studies are not ethical or feasible), and 21CFR601.91, approval based on evidence of effectiveness from studies in animals (under subpart H -approval of biological products when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 4

3. Species (common name) of animals used in this study: Canine

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

   These studies were performed to determine the toxicity of novel pharmaceutical/anticancer agents and set the groundwork for human clinical trials/use. During the course of these studies, unexpected toxicity occurred in 4 dogs. In these cases, animals were given supportive treatments and dosing was stopped or the animals were euthanized.

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.

   N/A

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:

   N/A