Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used in this study: 9

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

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

   The ferrets were subjected to an inhalation exposure of a classified compound of interest (COI). The inhalation exposure did cause more than momentary pain or distress in animals exposed to large amounts of the COI.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered without signs of distress; those with greater signs of distress were either unconscious after exposure or had reduced respirations prior to death. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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 in this study: 9

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

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

   The ferrets were subjected to an inhalation exposure of a classified compound of interest (COI). The inhalation exposure did cause more than momentary pain or distress in animals exposed to large amounts of the COI. This work included assessing the efficacy of a medical countermeasure.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered without signs of distress; those with greater signs of distress were either unconscious after exposure or had reduced respirations prior to death. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: 91

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

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

   The dosing procedure involved subcutaneous injection of a reversible acetylcholinesterase inhibitor which did not cause more than momentary pain or distress; however the resultant intoxication may have caused pain and/or distress including tremors, fasciculations and/or difficulty breathing. This work was conducted to determine the efficacy of a treatment regimen.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: 119

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

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

   The dosing procedure involved intramuscular administration of oximes which did not cause more than momentary pain or distress, and the subsequent intoxication caused either convulsions or lethargy and somnolence.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: 2251

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

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

   The dosing procedure involved dermal and subcutaneous administration which did not cause more than momentary pain or distress; however the resultant intoxication with select agent or other toxicants may have caused pain and/or distress including respiratory distress and fasciculations. This work was conducted to determine the most efficacious treatment.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: N/A. Note: This work was intended to support future definitive animal studies of therapeutic regimens (when human efficacy studies are not ethical or feasible).

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 100

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

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

The dosing procedure involved subcutaneous administration which did not cause more than momentary pain or distress; however the resultant intoxication with nerve agent may have caused pain and/or distress including tremors, fasciculations, respiratory distress and convulsions. This work was conducted to determine the optimum combination of treatments and dosages.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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:

   NA

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used in this study: 30

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

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

   Animals on study experienced intoxication induced by subcutaneous (SC) injection of a nerve agent. The exposure did cause more than momentary distress in animals exposed to large doses. Animals exhibiting mild clinical signs often recovered without signs of distress and those with signs of distress were either unconscious after exposure or had reduced respirations prior to death. This work was conducted to evaluate the effect of countermeasures.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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 in this study: 173

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 intravenous (IV) exposure of classified compounds of interest. The IV exposure did cause more than momentary distress in animals exposed to large doses. Animals exhibiting mild clinical signs often recovered without signs of distress and those with signs of distress were either unconscious after exposure or had reduced respirations prior to death.

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 or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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: 354

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

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

   Intradermal injection with bacterial spores. The dosing procedure involved an injection with select agent which did not cause more than momentary pain or distress. The resultant bacterial infection may have caused pain and/or distress including lethargy and /or respiratory distress in some animals. Some animals show no signs prior to being found dead. This work was conducted to evaluate challenge material used for countermeasure evaluations.

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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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 in this study: 39

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

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 with select agent itself is not painful but resultant bacterial infection may have caused pain and/or distress including lethargy and/or respiratory distress in some animals. Some animals showed no signs prior to being found dead. 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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: 6

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 anesthesia using a head-only exposure chamber. The challenge procedure with

select agent itself is not painful but resultant bacterial infection may have caused pain and/or distress including fever, lethargy and respiratory distress. This work was conducted to evaluate the efficacy of an antibiotic.

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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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: 33

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 spores. The challenge was performed under anesthesia using a head-only exposure chamber. The challenge procedure with select agent itself is not painful but resultant bacterial infection may have caused pain and/or distress including anorexia, fever, lethargy, weakness and respiratory 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: 33

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 spores. The challenge was performed under anesthesia using a head-only exposure chamber. The challenge procedure with select agent is not painful but resultant bacterial infection may have caused pain and/or distress including anorexia, fever, lethargy, weakness and respiratory 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: 6

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

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

   Explain the procedure producing pain and/or distress: Aerosol challenge with infectious bacteria. The challenge with select agent was performed under anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused more than momentary

pain and/or distress including lethargy, hunched posture, coughing, wheezing, labored breathing, prostration. This work was conducted to evaluate the efficacy of an antibiotic.

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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: Cynomolgus macaque

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

   Explain the procedure producing pain and/or distress: Aerosol challenge with infectious bacteria. The challenge with select agent was performed under anesthesia using a head-only exposure chamber. The challenge procedure itself is not painful but resultant bacterial infection may have caused more than momentary pain and/or distress including lethargy, hunched posture, coughing, wheezing, labored breathing, prostration.

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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: 10

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

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

   Aerosol administration of infectious virus. The challenge was performed under anesthesia. The challenge procedure with select agent did not cause more than momentary pain or distress but resultant viral infection may have caused more than momentary pain and/or distress including rash, labored respirations, respiratory distress, lethargy and prostration. This work was conducted to evaluate the effectiveness of 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: 10

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

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

   Aerosol administration of infectious virus or bacteria. The challenge was performed under anesthesia. The challenge procedure with select agent did not cause more than momentary pain or distress but resultant infection

may have caused more than momentary pain and/or distress including rash, hunched posture, coughing, labored breathing and lethargy. This work was conducted to evaluate the effectiveness of 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: 6

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

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

   Intravenous administration of infectious virus. The challenge was performed under anesthesia. The challenge procedure with select agent did not cause more than momentary pain or distress but resultant viral infection may have caused more than momentary pain and/or distress including rash, inappetance, dehydration and localized edema. This work was conducted to evaluate the effectiveness of 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, or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: Rhesus macaque

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

   Aerosol challenge with infectious bacteria. The challenge was performed under anesthesia using a head-only exposure chamber. The challenge procedure with select agent itself is not painful but resultant bacterial infection may have caused pain and/or distress including lethargy, respiratory distress, moribundity and other abnormal clinical observations. This work was conducted to develop an animal model which can be used in the future to test 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: 48

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

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

   Aerosol challenges with bacterial spores. The challenge procedure itself is not painful but resultant bacterial infection with select agent may have caused pain and/or distress including lethargy, respiratory distress in some animals and occasionally seizures. Some animals show no signs prior to being found dead. 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate or qualify a model and develop data necessary for definitive studies [that are required by the federal government under 21CFR.314.610 - 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: 325

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 procedure itself is not painful but resultant bacterial infection with select agent may have caused pain and/or distress including lethargy, respiratory distress in some animals and occasionally seizures. Some animals show no signs prior to being found dead. 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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: 87

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

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

   Intradermal injection. The dosing procedure itself did not cause more than momentary pain or distress but resultant viral infection with select agent may have caused pain and/or distress including rash, lethargy, fever and/or respiratory 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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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: 28

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

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

   Intradermal injection. The dosing procedure itself did not cause more than momentary pain or distress but resultant viral infection with select agent may have caused pain and/or distress including rash, lethargy, fever and/or respiratory distress. This work included a treatment.

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 or tranquilizers would be expected to alter the pathogenesis, signs/symptoms and/or progression of any resulting infectious process and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. Animals exhibiting clinical signs meeting euthanasia criteria per protocol or those which were moribund were euthanized to alleviate individual animal specific pain and distress. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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: New Zealand White rabbit

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

   Chemical agent administration. The dosing procedure involved dermal administration of advanced threat agents while the animals were anesthetized, which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress including convulsions, unresponsiveness and/or respiratory distress. The study was conducted to test the efficacy of a treatment (decontamination) regimen.

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.

   Analgesics, analgesics or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. This is especially important since the purpose of the study is to model human exposure. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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

   As appropriate, study conducted under Title 21, Food and Drugs, specifically, 21CFR.314.610, 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: 27

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

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

   Chemical agent administration. The dosing procedure involved IV administration of a classified compound of interest (COI) which did not cause more than momentary pain or distress, The resultant intoxication may have caused pain and/or distress including convulsions, unresponsiveness and/or respiratory 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.

   Analgesics, analgesics or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. This is especially important since the purpose of the study is to model human exposure. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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 validate a model and develop data necessary for definitive studies [required by the federal government under 21CFR.314.610 - 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: 27

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

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

   Chemical agent administration. The dosing procedure involved dermal administration of a classified compound of interest (COI) which did not cause more than momentary pain or distress, The resultant intoxication may have caused pain and/or distress including convulsions, unresponsiveness and/or respiratory 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.

   Analgesics, analgesics or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered. Animals exhibiting mild clinical signs often recovered without signs of distress and those with signs of distress exhibited ataxia, tremors and seizures. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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:

   NA

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 27

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

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

   Chemical agent administration. The dosing procedure involved inhalation administration which did not cause more than momentary pain or distress. The resultant intoxication may have caused pain and/or distress. The resultant intoxication may have caused pain and/or distress including convulsions, unresponsiveness and/or respiratory 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.

   Analgesics, analgesics or tranquilizers would be expected to mask the clinical appearance or potentiate the effects and thus confound results or invalidate the study. There are no known characterized, surrogate markers to predict mortality. Animals exhibiting mild clinical signs often recovered. Animals exhibiting mild clinical signs often recovered without signs of distress and those with signs of distress were either unconscious after exposure or had reduced respirations prior to death. Experienced staff veterinarians and animal technicians were on site to monitor the animal status and health during study conduct, and any potential animal welfare issues. The collection of scientifically robust animal safety and/or efficacy data were critical to the development of human risk assessments.

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:

   NA