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: Guinea pig

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

   The guinea pigs were subjected to an intravenous (IV) administration of compounds of interest. The IV compounds administered 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.

   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. The development of scientifically robust data was critical to the development of human safety data.

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

2. 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 guinea pigs were subjected to an intravenous (IV) administration of compounds of interest. The IV compounds administered 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 displayed prostration, unconsciousness, respiratory distress and ataxia. Some animals showed no signs prior to being found dead.

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. The development of scientifically robust data was critical to the development of human safety data.

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

3. Registration Number: 31-R-0021

2. Number of animals used: 131

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) administration of compounds of interest. The IV compounds administered 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 displayed prostration, unconsciousness, respiratory distress and ataxia. Some animals showed no signs prior to being found dead.

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. The development of scientifically robust data was critical to the development of human safety data.

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: 10

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

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

   Dermal administration of sulfur mustard (SM). The dermal SM challenge was performed under anesthesia. The challenge procedure with SM did not cause more than momentary pain or distress but resultant local and systemic toxicity may have caused more than momentary pain and/or distress including skin irritation, abnormal feces, lethargy, and mortality. This work was conducted to evaluate the effectiveness of Vitamin D treatment as a medical countermeasure to SM exposure.

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 injury process 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. 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 development of scientifically robust data was critical to the development of human safety data.

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: 11

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 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 hunched posture, coughing, labored breathing and lethargy. This work was conducted to evaluate the effectiveness of a therapeutic (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 development of scientifically robust data was critical to the development of human safety data.

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: Cynomolgus macaque

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

   Aerosol administration of infectious bacteria. The challenge was performed under anesthesia. 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 antibiotic treatment (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 development of scientifically robust data was critical to the development of human safety data.

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: 20

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

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

   Chlorine vapor inhalation in intubated swine. The challenge procedure with chlorine is not painful but resultant intoxication may have caused pain and/or distress including lethargy and/or respiratory distress in some animals. This work was conducted to develop an animal model to test efficacy of medical 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.

   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. The development of scientifically robust data was critical to the development of human safety data.

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: 14
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 intranasal (IN) administration of influenza A. The IN administration did not cause more than momentary distress in animals. Animals did exhibit mild clinical signs of disease, but none met euthanasia criteria.

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. The development of scientifically robust data was critical to the development of human safety data.

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: 91
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 intravenous (IV) administration of compounds of interest. The IV compounds administered did cause more than momentary distress in animals exposed to large doses. Animals that received vehicle-only or low doses often did not exhibit signs. 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.

   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. The development of scientifically robust data was critical to the development of human safety data.

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].