Column E Explanation Form

1. Registration Number: 31-R-0021
2. Number of animals used: 74
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 either GD, VX, or 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.

   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: 134
3. Species (common name) of animals used in this study: guinea pig
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 anorexia, fever, lethargy, weakness and respiratory distress. This work was conducted to evaluate the effectiveness of a vaccine (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:

   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: 56

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

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

   Intramuscular injection with a bacterial toxin. The challenge procedure itself is not painful but resultant toxicological effects may have caused pain and/or distress including lethargy and/or respiratory distress. This work was conducted to efficacy testing of a post-symptomatic therapeutic candidate.

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 systemic intoxication 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.

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 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: 161

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 compare the lethality of bacterial strains in an animal model to support risk modeling.

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.

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 study was not conducted per a CFR. This work was conducted to develop data to support modeling. This modeling is performed to understand the variability which might be observed in a potential real-world scenario in regard to observed lethality depending on the bacterial strain used.

Column E Explanation Form

1. Registration Number: 31-R-0021

2. Number of animals used: 12

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 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 a 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:

   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: 32

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

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, lethargy, weakness, respiratory abnormalities, fecal abnormalities, oral/nasal discharge, prostration, and unresponsiveness. 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:

   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.

Column E Explanation Form

1. Registration Number: 31-R-0021
2. Number of animals used: 12
3. Species (common name) of animals used in this study: Cynomolgus macaque
4. Explain the procedure producing pain and/or distress:

   Intramuscular challenge with bacterial toxin. The challenge procedure itself is not painful but resultant toxicological effects may have caused pain and/or distress including lethargy and/or respiratory distress. This work was conducted to efficacy testing of a post-symptomatic therapeutic candidate.

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.

   Bacterial toxins, by the nature of their mechanism of action, are considered paralytic agents. As the cause of death is respiratory failure, anesthetics cannot be used to alleviate distress as they also act as respiratory depressants that could potentiate the toxic action of the biological agent. Opioid analgesics and barbiturate sedative-hypnotics both cause respiratory depression. Benzodiazepines, while having fewer effects on respiration, have been shown to have substantial respiratory interactions when used in combination with other neuroleptic agents. Because of these side effects, anesthetics, analgesics, and sedatives could potentiate the toxicologic effects of the toxin and compromise the interpretation of study results.

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 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

Registration Number: 31-R-0021

2. Number of animals used: 26
3. Species (common name) of animals used in this study: Rhesus macaque
4. Explain the procedure producing pain and/or distress:

   The dosing procedure involved intramuscular administration of nerve agent and treatments 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 respiratory distress and fasciculations. This work was conducted to determine the efficacy of scopolamine in the nonhuman primate following nerve agent exposure and the pharmacokinetics of scopolamine in the absence of nerve agent 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.

   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 for eventual FDA licensure of scopolamine.

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/or 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].