Category E Explanation
Registration Number: 33-R-0008

1. A preclinical toxicology studies of two novel therapeutics to treat cancer resulted in substantial toxicity that resulted in an early termination of the study. Toxic effects included vomiting, diarrhea, and inactivity. Mortality occurred in one dog. Dogs were observed twice daily throughout the studies to identify toxic effects and to identify animals that should be euthanized *in extremis* due to the development of a moribund state (as defined by institutional Standard Operating Procedures). All dogs underwent a complete necropsy with tissue collection. Using data from these studies, it was determined to cancel all future studies.

2. In one preclinical toxicology study of a novel therapeutic agent for COVID-19, one dog experienced a severe reaction and was found dead. Dogs in this study were observed at least twice daily to identify animals that should be euthanized *in extremis* due to the development of a moribund state (as defined by institutional Standard Operating Procedures). The animal that was found dead underwent a complete necropsy with tissue collection and histopathological analysis. Data from this study helped define critical parameters supporting the selection of appropriate dose of the agents for use in clinical trials, and in identifying sensitive target organs that should be monitored in those trials.

   Analgesic agents cannot be administered in preclinical toxicology studies for the following reasons:

   - Many common analgesics (e.g., non-steroidal anti-inflammatory drugs) can alter the activity of enzymes involved in R, with resulting effects on agent Absorption, Distribution, Metabolism, and/or Excretion (ADME). For this reason, co-administration of analgesic agents in a preclinical toxicology study may have a significant impact on agent toxicity with resulting influences on study results.
   - Administration of analgesics may mask clinical signs of toxicity, and thereby reduce the sensitivity of the test system to identify toxicologic effects of mild to moderate severity.

   The animal species and group numbers used in the above toxicology studies were selected to meet published FDA and ICH standards for the design of preclinical safety assessments of novel therapeutic agents. Animal testing is required for preclinical safety assessments. The use of appropriate non-rodent test systems for preclinical toxicology studies is mandated by U.S. and international regulatory agencies, and no *in vitro* alternatives are accepted by these agencies. Furthermore, literature searches performed prior to the initiation of these studies were not successful in identifying alternate model systems that are both (a) scientifically rigorous and (b) acceptable to the FDA and other regulatory agencies.

Category E Explanation
Registration Number: 33-R-0008

1. In a preclinical study to determine the activity of a novel anti-infective agent, eight hamsters that received a challenge dose with COVID succumbed to infection. In this assay, prevention of virus-induced mortality and moribundity are key experimental endpoints used to evaluate agent efficacy.

   Analgesic agents cannot be administered in these studies for the following reasons:

   - Narcotic analgesics can cause histamine release (Soma, 1983, Nemzek *et al*., 2008) and induce respiratory depression that may alter the pathogenic and clinical responses to infection. These effects of narcotic analgesics could interfere with (and possibly invalidate) evaluations of antiviral activity.
   - Nonsteroidal anti-inflammatory drugs can also alter the pathogenesis of infection and clinical responses to anti-infective agents. Such effects could also invalidate evaluations of anti-viral potency.

   Prior to study initiation, a literature search was performed to identify alternate test systems that could generate efficacy data that are sufficient to: (a) support a rigorous scientific assessment of agent efficacy and (b) demonstrate evidence of agent efficacy that is sufficient to be accepted by the United States Food and Drug Administration (FDA). This literature search did not identify any alternate models suitable to replace the current *in vivo* assay.