

## COLUMN E EXPLANATION

1. **Registration Number:** 33-R-0008

2. **Number of animals used in these studies:** 80

Mortality was seen in two studies performed using dogs as an experimental model.

- The protocol for the first study included a total of 20 dogs. Three of 20 dogs from this study were found dead during the experimental period. Although no specific cause of death could be identified on the basis of clinical observations, gross pathology, or microscopic findings, the apparent cause of death in these animals was drug toxicity.
- The protocol for the second study included a total of 60 dogs. One dog in this study was found dead during the experimental period. Although no specific cause of death could be identified on the basis of clinical observations, gross pathology, or microscopic findings, the apparent cause of death in this animal was drug toxicity.

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

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

The goal of each study was to generate non-rodent toxicology data for a drug being developed for the treatment of infectious disease. Each study was performed to support one or more regulatory submissions to the United States Food and Drug Administration (FDA); data from these studies will be included in those regulatory submissions. Both studies were performed using protocols that are consistent with FDA requirements for preclinical toxicology studies in non-rodent species, and both studies were performed in full compliance with FDA Good Laboratory Practice Regulations.

Dogs were used in these studies in order to meet regulatory requirements for non-rodent toxicology studies, as defined by the FDA (see FDA *Redbook*). In both studies, dogs were observed at least twice per day for mortality, moribundity, or other clinical evidence of drug toxicity. In addition, body weight measurements, clinical pathology evaluations, and other endpoint evaluations were performed to identify and characterize any drug toxicity.

No clinical signs suggesting pain or distress were recorded in any of these dogs prior to their death. Extensive microscopic evaluations of tissues from these dogs also failed to identify a specific cause of death or any other disease indication that may have caused pain or distress. However, we are reporting these four dogs in Column E because we cannot be certain that they did not experience pain or distress prior to their death.

Use of analgesics or other pain relieving medications may interfere with drug distribution and/or metabolism, and would therefore interfere with the purpose of the study and the integrity of the data that was generated. For this reason, no analgesics or other pain relieving medications were administered to any animals during the study.