> proper conduct of nonclinical studies as published under 21 CFR Part 58 … [y]our firm did not check every animal cage for feed and water each day, or clean the animal cages for study (b)(4) for twelve days … [a]s a result, the animals were not checked (b)(4) as required in the *Animal Care Schedule* SOP.

To provide another example, the following Warning Letter complained about the Sponsor's *failure to analyze a specimen* from a test animal (130):

> Dear Mr. [REDACTED]:
>
> FDA investigator … met with … members of your staff to review your firm's conduct of study [REDACTED] performed under the Good Laboratory Practices (GLP) regulations [21 CFR Part 58] … [a]t the end of the inspection, a Form FDA 483 … was issued and discussed with … your staff … [t]hese specimens represent eight of the … animals in one of the … dose cohorts required for … studies at the … week time point. The box packed on 12/8/05 was not found until almost one year later during the FDA inspection. The final report for study … was signed by the study director on 04/06/06 with no indication that these samples were missing, as evidenced by the lack of protocol deviation report in the study file. Your letter acknowledges that these samples were not analyzed. You explain that these animals were administered an [REDACTED] test article dose and were not included in the final study report. We disagree with your claim that these samples had no bearing or impact on the study data.

h. Animal Rule

Where a Sponsor seeks FDA approval of a drug, but where use of human subjects would be unethical, the FDA permits use of animal model data as the basis for approval for administration in humans. For example, FDA approval for treatments for plague due to *Yersinia pestis* was granted using the African green monkey model, approval for a treatment for cyanide poisoning was granted using a dog model, and approval for a treatment for smallpox (variola virus) was granted using monkeypox virus in primates and rabbitpox in rabbits (131). To provide another example, the FDA has also described the hypothetical treatment of a drug to treat gastrointestinal disorders resulting from acute radiation exposure in the case of a nuclear detonation (132).

This avenue for drug approval is called the Animal Rule. The Animal Rule finds a basis in Sections 314.600 (small molecule drugs) and 601.90 (biologicals) of the Code of Federal Regulations. According to the FDA's Guidance for Industry (133):

> The Animal Rule states that for drugs developed to ameliorate or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic substances, when human challenge studies would not be ethical to perform and field trials to study effectiveness after accidental or intentional human exposure have not been feasible, FDA may grant marketing approval based on adequate and well-controlled animal efficacy studies when the results of those studies establish that the drug is reasonably likely to produce clinical benefit in humans.

In addition to the requirement that use of human subjects not be ethical, the FDA requires that the mechanism of action of the disorder in the animal model correspond to the mechanism of action of the disorder in humans, and that the mechanism of action of the proposed treatment in the animal model

[130]Warning Letter, CBER-07-007, March 23, 2007.

[131]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Product development under the animal rule; May 2014 (53 pp.).

[132]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Product development under the animal rule; May 2014 (53 pp.).

[133]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Product development under the animal rule; May 2014 (53 pp.).