conducted in compliance with the requirements set forth in 21 CFR Part 58" (123). The FDA has commented on the frequency of RTF decisions, where these decisions are based on a number of problems, not merely on issues in test animals that occur in nonclinical studies (124).

GLP is applied, for example, to in vivo mutagenicity studies, acute toxicity studies, chronic toxicity studies, and carcinogenicity studies. However, GLP does not apply to clinical studies, or to studies on veterinary drugs in animals (125). A quality assurance manager, quality control analysts, and standard operating procedures (SOPs), are used in laboratories operating under GLP (126).

g. Examples of FDA Form 483 Warning Letters, as Applied to Animal Studies

FDA Form 483 warning letters are available on the FDA's website. Problems relating to animals are only one of the many problems that can provoke the FDA to issue a Form 483. Please note the following. Although Form 483 letters are available on the FDA's website device that is called, "Warning Letters," it is not the case that Form 483 is exactly the same thing as a Warning Letter. Form 483 letters are issued with a minimal amount of review while, in contrast, Warning Letters are issued by the FDA only after high-level review by attorneys employed by the FDA (127). It is common for Form 483 to be referred to as a "warning letter" (128). For convenience, the present commentary refers to Form 483 as a "warning letter."

The following Warning Letter complained about the Sponsor's *failure to clean animal cages*. The Warning Letter refers to a SOP, and to the failure of the Sponsor to comply with this particular SOP (129):

> Dear Dr. [REDACTED]:
>
> The FDA investigators met with you and other members of your staff to review [your] Corporation's conduct of nonclinical laboratory studies ... performed under the Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies regulations [21 CFR Part 58] ... [a]t the end of the inspection a Form FDA 483, Inspectional Observations, was issued and discussed with you ... we conclude that [your company] has violated GLP regulations governing the

[123]U.S. Department of Health and Human Services. Food and Drug Administration. Manual of policies and procedures. Good review practice: refuse to file; October 11, 2013 (21 pp.).

[124]According to Janet Rehnquist, "[a]lthough FDA can refuse to file applications, it rarely does so. The CDER refused to file 4 percent of submitted applications in FY 2000, down from 17 percent in 1993. In part, this decrease may be attributable to the advice FDA provides sponsors that helps them prepare higher quality applications." See, Rehnquist, J. FDA's review process for new drug applications. A management review. Department of Health and Human Services; March 2003 (47 pp.).

[125]Adamo JE, Bauer G, Berro M, et al. A roadmap for academic health centers to establish good laboratory practice-compliant infrastructure. Acad. Med. 2012;87:279–84.

[126]Adamo JE, Bauer G, Berro M, et al. A roadmap for academic health centers to establish good laboratory practice-compliant infrastructure. Acad. Med. 2012;87:279–84.

[127]According to Cooper and Fleder, "[a] #483 is issued by one or more FDA investigators at the conclusion of a site inspection, and usually is not reviewed by a compliance officer, district director, or an official in FDA's headquarters before it is issued. An FDA warning letter, on the other hand, is issued by a district director or headquarters official of similar seniority, and only after review by FDA's Office of Chief Counsel." See, Cooper RM, Fleder JR. Responding to a Form 483 Warning Letter: a practical guide. Food Drug Law J. 2005;60:479.

[128]Senger JM. Emerging issues in FDA regulation: warning Letters, internet promotion, and tobacco. J. Health Care Policy 2010;13:211–25.

[129]Warning Letter, CBER-09-01, January 5, 2009.