> intervals … [f]eed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

To give another example about animal care, 21 CFR §58.120 sets forth requirements about written protocols, records of test articles (drugs), animal weight, and diet:

> Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain … [i]dentification of the test and control articles by name, chemical abstract number, or code number … [t]he number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system … [a] description and/or identification of the diet … [e]ach dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration.

Thus, it is self-evident that GLP encompasses a number of topics relating to the Sponsor's laboratories. These topics overlap those used in basic research, but with the following exception. In basic research, laboratory procedures are likely to change every month, in response to experimental results. However, GLP allows for little flexibility and hence is not compatible with most types of basic research.

If a sponsor is found not to comply with GLP, then the FDA may respond by disqualifying a testing facility (21 CFR §58.202). Grounds for disqualification include a situation where noncompliance adversely affects the validity of the animal studies or any other nonclinical laboratory studies, or where the Sponsor ignores warnings from the FDA.

The term "483" is known throughout the pharmaceutical industry (120). Following an inspection of a testing facility by FDA officials, the FDA may issue a warning on a document called, Form FDA-483. The nature of Form FDA-483 is as follows (121):

> The FDA-483 is the written notice of objectionable practices or deviations from the regulations that is prepared by the FDA investigator at the end of the inspection. The items listed on the form serve as the basis for the exit discussion with laboratory management at which time management can either agree or disagree with the items and can offer possible corrective actions to be taken.

Regarding validation of each written protocol, it is the case that the FDA acknowledged the need for flexibility in how the Sponsor establishes validity. To this end, the FDA's Guidance for Industry states that (122):

> Who assesses protocol validity (Number of animals, test article dosage, test system, etc.)? This is done by the study scientists using the scientific literature, published guidelines, advice from regulatory agencies, and prior experimental work.

If a Sponsor submits data from animal studies, as part of an FDA submission, the FDA may respond by sending a RTF notice to the Sponsor. According to the FDA's *Manual of Policies and Procedures*, the FDA issues a RTF if, "[t]he application does not contain a statement for each nonclinical laboratory study that it was

[120]Pritchett T. A 483 Primer. Learning from the mistakes of others. BioProcess Int.; March 2011 (4 pp.).

[121]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Good laboratory practices questions and answers; July 2007 (25 pp.).

[122]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Good laboratory practices questions and answers; July 2007 (25 pp.).