that was created with recombinant technology is the "Harvard Mouse," which is a mouse engineered to express an oncogene, such as the *c-myc* gene (116).

The European Medicines Agency (EMA) has provided guidance for assessing the validity of a given animal model for use in testing the efficacy of a drug for a particular disease. According to the EMA (117):

> Qualitative and quantitative differences may exist in biological responses in animals compared to humans. For example, there might be differences in affinity for molecular targets, tissue distribution of the molecular target, cellular consequences of target binding, cellular regulatory mechanisms, metabolic pathways, or compensatory responses to an initial physiological perturbation.

## e. Validation of Animal Models

After an animal model has been identified or developed, one can establish the validity of that model by way of the process of "validation." According to Varga et al. (118), validating an animal model includes development of a particular procedure or test that uses a specific type of animal, followed by employing the laboratory procedure, independently conducted in a blind trial, by at least three different laboratories. This interlaboratory trial is followed by data analysis and an evaluation of the outcome of the study in comparison with predefined performance criteria. The final step in validation may take the form of acceptance by a regulatory agency, such as a national or international organization.

## f. GLP, as It Applies to Animal Studies

GLP is a set of standards set forth by the FDA.

Before the FDA grants approval to a Sponsor to initiate recruiting of human subjects and to conduct a clinical trial, the Sponsor is required to submit nonclinical safety and toxicology studies to demonstrate that the proposed drug entity is likely to be safe with testing in a clinical trial on human subjects. The term "nonclinical studies" encompasses studies with animals, in vitro cell culture, and the Ames bacterial mutagenicity test. These nonclinical studies are governed by GLP regulations (119). GLP is regulated by Title 21 CFR §58. Title 21 CFR §58 is entitled, "Good Laboratory Practice for Nonclinical Laboratory Studies." If there are deficiencies in GLP, for example, in the maintenance of the animal facility, the FDA may issue a *Refuse to File* (RTF) notice. The consequence of the RTF notice is that the FDA halts any further review of the Sponsor's application, until the Sponsor takes appropriate remedial action. Title 21 CFR §58 provides concrete guidance on what is required for animal studies. For example, 21 CFR §58.90 sets forth requirements for animal care:

> Animal cages, racks and accessory equipment shall be cleaned and sanitized at appropriate

[116]Pattengale PK, et al. Animal models of human disease. Pathology and molecular biology of spontaneous neoplasms occurring in transgenic mice carrying and expressing activated cellular oncogenes. Am. J. Pathol. 1989;135:39–61.

[117]European Medicines Agency. Committee for Medicinal Products for Human Use (July 2007) Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicine Products (12 pp.).

[118]Varga OE, et al. Validating animal models for preclinical research: a scientific and ethical discussion. Alternat. Lab Anim. 2010;38:245–8.

[119]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.