

collagen (95). A mouse model for inflammatory bowel disease employs a strain of mice that naturally develops inflammation of the intestinal tract (96). Psoriasis (97), lupus (98), asthma (99), and other immune disorders also have well-characterized animal models.

## b. FDA Regulations and Animal Models

Animal models are used to provide data on safety and efficacy, where the data are included in various FDA submissions. Relevant issues include:

- disease mechanisms,
- validation,
- good laboratory practice (GLP),
- animal rule.

Animals are used in the following situations. The first is for discovering the mechanisms of a disease. Second, animals are used for discovering the mechanisms of drug action (with or without regard to any disease). In other words, the ability of the anticancer drug *ibrutinib* to inhibit Bruton's tyrosine kinase can be studied in noncancerous cells, as well as in cancer cells (100). Third, the issue of animals arises when there is a need to develop a suitable animal model for a disease. Fourth, the issue of animals occurs in the validation of an existing animal model for a disease. And fifth, the issue of animals occurs when

conducting animal studies in compliance with GLP. GLP governs many laboratory practices in addition to those involving animals. The following comments also disclose adverse consequences to a Sponsor, where the Sponsor's use of animals fails to comply with various FDA regulations, as set forth by 21 CFR §58 and by GLP.

## c. Disease Mechanisms

An animal model may be ideally suited for determining the mechanism of a disease, and for the screening of candidate drugs, but may be inappropriate and ill-suited for determining efficacy or safety of a particular type of therapy for that disease. The fruitfly is one type of an animal model that is not likely to be accepted by the FDA, for convincing the FDA of a drug's efficacy and safety. The proven utility of the fruitfly model is as follows. According to Poidevin et al. (101), the fruitfly *Drosophila melanogaster* is:

a premiere model system for the study of human neurodegenerative diseases, due to the realization that flies and humans share many structurally and functionally related gene families. Development of such disease models in the fly allows ... the existing fruit fly models of human neurological disorders to identify small-molecule leads that could potentially be further developed for therapeutic use.

<sup>95</sup>Cho YG, Cho ML, Min SY, Kim HY. Type II collagen autoimmunity in a mouse model of human rheumatoid arthritis. *Autoimmun. Rev.* 2007;7:65–70.

<sup>96</sup>Wilk JN, Bilsborough J, Viney JL. The *mdr1a*<sup>-/-</sup> mouse model of spontaneous colitis: a relevant and appropriate animal model to study inflammatory bowel disease. *Immunol. Res.* 2005;31:151–9.

<sup>97</sup>Schön MP. Animal models of psoriasis: a critical appraisal. *Exp. Dermatol.* 2008;17:703–912.

<sup>98</sup>Cohen PL, Maldonado MA. Animal models for SLE. *Curr. Protoc. Immunol.* 2003;Chapter 15:Unit 15.20.

<sup>99</sup>Takeda K, Gelfand EW. Mouse models of allergic diseases. *Curr. Opin. Immunol.* 2009;21:660–5.

<sup>100</sup>Woyach J, Furman RR, Liu TM, et al. Resistance mechanisms for Bruton's tyrosine kinase inhibitor ibrutinib. *New Engl. J. Med.* 2014;370:2286–94.

<sup>101</sup>Poidevin M, et al. Small-molecule screening using *Drosophila* models of human neurological disorders. *Methods Mol. Biol.* 2015;1263:127–38.