Moreover, Pandey and Nichols (102) state that the fruitfly is useful for determining the mechanisms and for drug screening for a variety of human disorders. According to these authors, the fruitfly:

> can effectively be used for … high-throughput drug screens as well as in target discovery … [and for] models of human diseases and opportunities for therapeutic discovery for central nervous system disorders, inflammatory disorders, cardiovascular disease, cancer, and diabetes.

Guidance on why certain animal models are not appropriate for establishing efficacy of any given drug comes from an agency of the US government other than FDA, namely, the US Patent and Trademark Office (USPTO). From the USPTO, superlative and consistent guidance on certain issues is provided by the Patent Trial and Appeal Board (PTAB). This guidance takes the form of many thousands of published opinions from the Board, for example, *Ex parte Steffan* (103).

*Ex parte Steffan* concerned a proposal to treat a human disease (Huntington's disease) with a drug, where this proposal was based on data from an animal model. The animal model was a genetically altered fruitfly. In the fruitfly study, the investigators discovered that the neurological disease in the fruitfly could be cured by mutating one of the fruitfly's genes. The gene was the *smt3* gene. The mutation in the *smt3* gene suppressed neurodegeneration in the fruitfly, just as the eventual goal of the investigators was to suppress neurodegeneration in human patients. The Patent Office refused to accept the fruitfly model as a suitable model for treating Huntington's disease in humans. The reasons for refusing to accept the fruitfly model include the following:

- Invertebrates models are unpredictable.
- Drugs cannot be administered to flies. Please note that invertebrates have an open circulatory system, and do not have any arteries or veins (104).
- The method that successfully prevented the disease in the fruitflies (mutating the *smt* gene in the chromosome) cannot be performed on human patients.
- Mammalian animal models are closer to humans than invertebrates. The Patent Office stated that, "non-human mammals … more closely replicate the essential features of the pathophysiology of the disease in humans, as compared to invertebrate models" (105).

In a similar published opinion from the Board, the Board considered the ability of a genetically modified mouse to be a model for treatment of human degenerative diseases. As described in *Ex parte Franzoso* (106) the genetically modified mouse was engineered to have a mutation in the *Gadd45beta* gene. The eventual goal of the investigators was to develop an administrable drug that inhibits the *Gadd45beta* gene in humans. However, the Board refused to accept the mouse model.

[102]Pandey UB, Nichols CD. Human disease models in *Drosophila melanogaster* and the role of the fly in therapeutic drug discovery. Pharmacol. Rev. 2011;63:411–36.

[103]*Ex parte* Steffan, No. 2009-005999 (B.P.A.I. Mar. 2, 2010).

[104]Brody T, Mathews TD. The release of zinc from leukocytes provoked by A23187 and EDTA is associated with the release of enzymes. Comp. Biochem. Physiol. Part A 1989;94:693–7.

[105]Examiner's Answer of Aug. 5, 2008, at 7, in file history of U.S. Patent Application No. 10/789,518.

[106]*Ex parte* Franzoso, No. 2007–2724 (B.P.A.I. Mar. 12, 2008).