reaction in animals must resemble that occurring in humans (220,221). Animal models for idiosyncratic drug reactions include the "nevirapine-induced skin rash" test in rats (222). Please note that, in humans, nevirapine can result in SJS and liver toxicity. The acetaminophen-induced liver injury test in mice is a model for liver toxicity. The halothane-induced liver injury test in guinea pigs is another model. The clozapine-induced hematological toxicity test in rats has been used to study the idiosyncratic drug reaction taking the form of agranulocytosis (223).

Sulfamethoxazole-induced hypersensitivy in dogs and the penicillamine-induced reaction in rats are additional animal models (224). This example provides a context for all types of animal models that are intended for use in FDA-regulated drug development. According to Adamo et al. (225) basic exploratory studies do not have to following FDA's regulations on Good Laboratory Practice (GLP), but GLP regulations "do apply to subsequent safety and toxicology studies" that are intended for FDA-submission. Further information on GLP is cited (226,227).

VI. FDA'S DECISION-MAKING PROCESS IN EVALUATING ADVERSE EVENTS

a. FDA's Decision-Making Process in Evaluating Ipilimumab, and Stevens-Johnson Syndrome

This is from FDA's approval of *ipilimumab*, for the indication of melanoma. This example is from biologics license application (BLA) 125377, at Mar. 2015 of FDA's website. The FDA reviewer commented on the adverse event of SJS, writing that:

> [s]evere, life-threatening or fatal immune-mediated dermatitis (eg, Stevens–Johnson syndrome … occurred in 13 (2.5%) YERVOY-treated patients … [o]ne … patient died as a result of toxic epidermal necrolysis and one additional patient required hospitalization for severe dermatitis.

As a consequence of this adverse reaction, the Sponsor wrote and submitted a REMS to the FDA, and agreed to transmit this REMS to all physicians who are members of several

[220]Shenton JM, et al. Animal models of idiosyncratic drug reactions. Chem.-Biol. Interactions 2004;150:53–70.

[221]Brody T. Enabling claims under 35 USC §112 to methods of medical treatment or diagnosis, based on in vitro cell culture models and animal models. Journal Patent Trademark Office Society; 2015 (in press).

[222]Ng W, Lobach AR, Zhu X, et al. Animal models of idiopathic drug reactions. Adv. Pharmacol. 2012;63:81–135.

[223]Ng W, Lobach AR, Zhu X, et al. Animal models of idiopathic drug reactions. Adv. Pharmacol. 2012;63:81–135.

[224]Shenton JM, et al. Animal models of idiosyncratic drug reactions. Chem.-Biol. Interactions 2004;150:53–70.

[225]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.

[226]The Code of Federal Regulations includes a section on Good Laboratory Practice (GLP), namely, 21 CFR §58. For example, 21 CFR 58.120 requires that, "[e]ach study shall have an approved written protocol that … shall contain … [a] description … of the diet in the study … each dosage level, expressed in milligrams per kilogram of body weight."

[227]Lee CS, Lee JY. Good Laboratory Practice (GLP) regulations: interpretation techniques and review of selected compliance issues. Drug Infor. J. 2006;40:33–8.