Contraindications section of the package insert, "[o]rdinarily, a drug should be contraindicated on the basis of an anticipated adverse reaction if the risk of the adverse reaction in the clinical situation ... based on both likelihood and severity of the adverse reaction, outweighs any potential benefit to any patents ... and ... animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans" (68). In other words, the information on *Contraindications* should be disclosed only where risk outweighs the benefit of the drug.

b. FDA's Decision-Making Process in Evaluating Animal Toxicity Data and Information on the Package Insert

This concerns the drug approval process for dimethyl fumarate (DMF), for treating multiple sclerosis. The information is from the Medical Review for NDA 204063, on Mar. 2013 of the FDA's website. The FDA reviewer observed that, "DMF is toxic to the kidney in multiple species. Renal pathology, including tubular basophilia, tubular dilation, nephropathy ... were seen in the rat ... similar findings were seen in the dog ... [i]n a one year monkey study, tubular necrosis and regeneration were also seen."

Regarding the labeling recommendations, the FDA reviewer wrote, "Please refer to approved label." A view of the package insert reveals information regarding renal toxicity (69). This information does not occur in the *Warnings and Precautions* section of the package insert. The information does not occur in the *Contraindications* section. Instead, it occurs in the *Animal Toxicology and/or Pharmacology* section of the package insert, where it reads:

> Kidney toxicity was observed after repeated oral administration of dimethyl fumarate (DMF) in mice, rats, dogs, and monkeys. Renal tubule epithelia regeneration, suggestive of tubule epithelial injury, was observed in all species.

The take-home lesson is that, where safety data from animals are available, the Sponsor should ensure that the relevant information is properly included in the package insert in one or more of the *Warnings and Precautions* section, the *Contraindications* section, and the *Animal Toxicology and/or Pharmacology* section.

FDA refrained from requiring that the package label disclose renal toxicity issues in the *Warnings and Precautions* section, and in fact, the FDA reviewer stated that, "the clinical trials did not suggest that [study drug] ... exposed patients were at increased risk for renal toxicity."

However, FDA went a step further by disclosing the Sponsor's agreement to conduct additional studies on renal toxicity in patients taking the marketed drug. Referring to this agreement, the reviewer wrote that, "the Sponsor states that they intend to conduct a large, global, observational study with the ... objective of determining the nature and incidence of ... serious renal ... events." The take-home lesson is as follows. Where a gray area occurs as to toxicity issues, the Sponsor may choose to include information in the *Animal Toxicology and/or Pharmacology* section, and also to conduct additional studies after the drug goes on the market.

[68]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Warnings and precautions, contraindications, and boxed warning section of labeling for human prescription drug and biological products—Content and Format; October 2011 (13 pp.).

[69]Package insert for TECFIDERA (dimethyl fumarate) delayed-response capsules for oral use; March 27, 2013 (12 pp.).