The following provides the scientific background on how drugs can provoke increases in serum bilirubin. Bilirubin in the bloodstream may be taken up by way of the organic anion transporter proteins OATP1B1 and OATP1B3. It is recognized that genetic diseases that impair activity of OATP1B1 transporters can provide increases in serum bilirubin, as well as exacerbate the toxicity of drugs (methotrexate, statin drugs) that are cleared from the bloodstream by way of these transporters (65). Thus, the FDA's reviewer's comments about vedroprevir can be seen as a reasonable explanation for the observed adverse event of increased bilirubin.

IV. SUMMARY OF DRUG–DRUG INTERACTIONS

Information on drug–drug interactions is required on the package insert of FDA-approved drugs. Sponsors conduct drug–drug interaction studies using purified enzymes, subcellular particles such as microsomes, in vitro cultured cells, animal studies, and studies on human subjects. Information on drug–drug interactions, as well as on drug–food interactions, may be included in the *Medication Guide*. Most typically, the enzyme of interest is one or more of the cytochrome P450 enzymes.

Because of the heterogeneity of genes encoding the drug-metabolizing enzymes and transport systems, in the human population, biomarkers have been devised to identify variants in these genes. Where a variant has been identified in an enzyme that metabolizes the study drug, or in a transport system, and if this variant changes the rate of metabolism or transport, corresponding information may be placed in the *Warnings and Precautions* section of the package insert.

V. ANIMAL TOXICITY DATA AND THE PACKAGE INSERT

a. Animal Toxicity Data and FDA's Guidance for Industry

Safety data from animal studies can be included in the package insert, even in the absence of corresponding safety data from human subjects. This concerns the *Warnings and Precautions* section and the *Contraindications* section of the package insert.

Regarding package inserts, FDA's Guidance for Industry provides advice for adverse reactions that have not been observed in humans. For these adverse reactions, FDA recommends that, "[t]he Warnings and Precautions section should include serious or otherwise clinical significant adverse reactions ... that are anticipated to occur with the drug if ... animal data raise substantial concern about the potential for occurrence of the adverse reaction in humans ... e.g., animal data demonstrating that a drug has teratogenic effects" (66). Consistent with this, is the fact that researchers have commented on the fact that, "serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data" (67).

FDA's Guidance for Industry provides a similar recommendation for the

[65]Sticova E, Jirsa M. New insights in bilirubin metabolism and their clinical implications. World J. Gastroenterol. 2013;19:6398–407.

[66]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.).

[67]Halloran K, Barash PG. Inside the black box: current policies and concerns with the United States Food and Drug Administration's highest drug safety warning system. Curr. Opin. Anaesthesiol. 2010;23:423–27.