the *Warnings and Precautions* part of the package insert disclose the drug's interference with laboratory tests:

> (iv) *Interference with laboratory tests*. This section must briefly note information on any known interference by the product with laboratory tests and reference the section where the detailed information is presented (e.g., "Drug Interactions" section).

Characterizing drug–drug interactions includes in vitro studies to see whether a drug is a substrate, inhibitor, or inducer of enzymes that metabolize drugs. Enzymes that metabolize drugs include those that catalyze drug oxidation, as well as those catalyzing conjugation with sugars, sulfate groups, and so on. Various isozymes of cytochrome P450 are the most commonly studied of these enzymes, and these isozymes include cytochrome P450 enzymes known by the abbreviations:

- CYP1A2;
- CYP2B6;
- CYP3A.

Other enzymes and proteins that are the subject of drug–drug interaction studies include uridine diphosphate (UDP)-glucuronosyltransferase, as well as transport proteins such as:

- BCRP;
- OATP1B1;
- OTP1B3.

FDA's Guidance for Industry describes the isozymes of cytochrome P450, drug conjugating enzymes, and transport systems, as well as some of the more notorious examples of drug–drug interactions (35).

b. Instructions in a Clinical Study Protocol That Prohibit Concomitant Drugs

The issue of drug–drug interactions is so prevalent that the Clinical Study Protocol may include instructions that prohibit study subjects from taking certain medications that are expected to modify in vivo metabolism of the study drug.

The following provides a set of instructions that are somewhat generic, in view of the fact that the pharmacokinetics of the drug was only partly characterized. The excerpt is from a Protocol on prostate cancer. The warning refers to a list in an appendix in the Protocol (36,37):

> APPENDIX G provides a list of potent CYP enzyme inhibitors and inducers that may have a theoretical concern of potential drug–drug interactions with [the study drug]. In vitro drug metabolism studies suggest that [the study drug] may have the potential to induce CYP3A4 and to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; therefore, concomitant medications that are substrates of any of these enzymes should be used with caution, and relevant monitoring should be considered, especially for substrates known to cause seizure, because the possibility of drug–drug interactions cannot be fully excluded. Since the metabolism of [the study drug] is not known, caution should be taken for the

[35]U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Drug interaction studies—study design, data analysis, implications for dosing, and labeling recommendations; February 2012 (75 pp.).

[36]Clinical Research Protocol. Study Title: PREVAIL: A multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy protocol no: MDV3100-03.

[37]Clinical Study Protocol available as supplement to: Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. New Engl. J. Med. 2014;371:424–33.