after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period.

The black box warning for sertraline (34) reads, in part:

WARNING. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Zoloft or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

II. DRUG–DRUG INTERACTIONS

a. Introduction

The term "drug–drug interactions" concerns a first drug's influence on the metabolism of a second drug. For example, the first drug can influence parameters of the second drug, such as its plasma concentration, rate of transport into cells, rate of efflux out of cells, rate of catabolism, and rate of conjugation. Where drug–drug interactions have been found for a study drug, issues that can arise include unexpected changes in the safety and efficacy of the drug. For these reasons, package inserts for drugs include a section entitled, "Drug–drug interactions." Drug–drug interactions find a basis in 21 CFR §201.57, which requires the following. The emphasis is added:

> (8) ***Drug interactions***. (i) This section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or **foods** (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. The mechanism(s) of the **interaction**, if known, must be briefly described. Interactions that are described in the "Contraindications" or "Warnings and Precautions" sections must be discussed in more detail under this section.

Please note that the influences of *foods* on the study drug should be included in the *Drug–Drug Interactions* section of the package insert. A concrete example of food–drug interactions is provided below, in the account of *everolimus*. Further regarding drug–drug interactions, the *Dose and Administration* part of the package label requires a disclosure of (21 CFR §201.57):

> (H) Modification of dosage needed because of **drug interactions** or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease).

A concept related to drug–drug interactions is the interference of the study drug with a laboratory test. Section 201.57 also requires that

[34]Package insert. Pfizer, Zoloft (October 2008).