

(b) For prescription drugs for human use containing FD&C Yellow No. 5 that are administered orally, nasally, vaginally, or rectally, or for use in the area of the eye, the labeling required by § 201.100(d) shall bear the warning statement “This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.” This warning statement shall appear in the “Precautions” section of the labeling.

(c) The label for over-the-counter drug products intended for human use administered orally, nasally, rectally, or vaginally containing FD&C Yellow No. 6 shall specifically declare the presence of FD&C Yellow No. 6 by listing the color additive using the name FD&C Yellow No. 6. The labeling for over-the-counter and prescription drug products containing FD&C Yellow No. 6 shall declare the presence of FD&C Yellow No. 6. The labels of certain drug products subject to this labeling requirement that are also cosmetics, such as antibacterial mouthwashes and fluoride toothpastes, need not comply with this requirement provided they comply with the requirements of § 701.3 of this chapter.

[45 FR 60422, Sept. 12, 1980, as amended at 51 FR 41783, Nov. 19, 1986; 52 FR 21509, June 8, 1987; 59 FR 60898, Nov. 29, 1994]

EFFECTIVE DATE NOTE: At 53 FR 49138, Dec. 6, 1988, § 201.20(c) was suspended pending further agency action.

**§ 201.21 Declaration of presence of phenylalanine as a component of aspartame in over-the-counter and prescription drugs for human use.**

(a) Aspartame is the methylester of a dipeptide composed of two amino acids, phenylalanine and aspartic acid. When these two amino acids are so combined to form aspartame (1-methyl *N*-L- $\alpha$ -aspartyl-L-phenylalanine), they produce an intensely sweet-tasting substance, approximately 180 times as sweet as sucrose. The Food and Drug Administration has determined that aspartame when used at a level no

higher than reasonably required to perform its intended technical function is safe for use as an inactive ingredient in human drug products, provided persons with phenylketonuria, who must restrict carefully their phenylalanine intake, are alerted to the presence of phenylalanine in the drug product and the amount of the ingredient in each dosage unit.

(b) The label and labeling of all over-the-counter human drug products containing aspartame as an inactive ingredient shall bear a statement to the following effect: Phenylketonurics: Contains Phenylalanine ( )mg Per (Dosage Unit).

(c) The package labeling and other labeling providing professional use information concerning prescription drugs for human use containing aspartame as an inactive ingredient shall bear a statement to the following effect under the “Precautions” section of the labeling, as required in § 201.57(f)(2): Phenylketonurics: Contains Phenylalanine ( )mg Per (Dosage Unit).

(d) Holders of approved new drug applications who reformulate their drug products under the provisions of this section shall submit supplements under § 314.70 of this chapter to provide for the new composition and the labeling changes.

(Approved by the Office of Management and Budget under control number 0910-0242)

[52 FR 2111, Jan. 20, 1987; 52 FR 12152, April 15, 1987; 53 FR 4135, Feb. 12, 1988]

**§ 201.22 Prescription drugs containing sulfites; required warning statements.**

(a) Sulfites are chemical substances that are added to certain drug products to inhibit the oxidation of the active drug ingredient. Oxidation of the active drug ingredient may result in instability and a loss of potency of the drug product. Examples of specific sulfites used to inhibit this oxidation process include sodium bisulfite, sodium metabisulfite, sodium sulfite, potassium bisulfite, and potassium metabisulfite. Recent studies have demonstrated that sulfites may cause allergic-type reactions in certain susceptible persons, especially asthmatics.