

§ 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. The labeling for any prescription drug product to which sulfites have been added as an inactive ingredient, regardless of the amount added, must bear the warning specified in paragraph (b) or (c) of this section.

(b) The labeling required by §§ 201.57 and 201.100(d) for prescription drugs for human use containing a sulfite, except epinephrine for injection when intended for use in allergic or other emergency situations, shall bear the warning statement "Contains (*insert the name of the sulfite, e.g., sodium metabisulfite*), a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people." This statement shall appear in the "Warnings" section of the labeling.

(c) The labeling required by §§ 201.57 and 201.100(d) for sulfite-containing epinephrine for injection for use in allergic emergency situations shall bear the warning statement "Epinephrine is the preferred treatment for serious allergic or other emergency situations even though this product contains (*insert the name of the sulfite, e.g., sodium metabisulfite*), a sulfite that may in other products cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using

epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite(s) in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations." This statement shall appear in the "Warnings" section of the labeling.

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§ 201.23 Required pediatric studies.

(a) A manufacturer of a marketed drug product, including a biological drug product, that is used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients, as defined in §§ 314.55(c)(5) and 601.27(c)(5) of this chapter, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may by order, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within a