(a) Combination drug products containing an expectorant and an oral antitussive that is also an antihistamine. The Panel recommended a Category I classification for combinations containing an oral antitussive and an expectorant that is labeled for nonproductive cough (41 FR 38312 at 38328). The agency concurred in the tentative final monograph for OTC cough-cold combination drug products (53 FR 30522 at 30556). However, the Panel recommended a Category II classification for combinations containing an antihistamine and an expectorant. In this combination, the anticholinergic effect (drying action) of the antihistamine would produce the opposite effect of the secretory action of the expectorant ingredient. Thus, the combination would be medically irrational (41 FR 38312 at 38326). The agency concurred with the Panel in the OTC cough-cold combinations tentative final monograph (53 FR 30522 at 30556). Because diphenhydramine is an antihistamine as well as an antitussive, it would have anticholinergic effects whether it is included in a combination as an oral antitussive or as an antihistamine. Accordingly, the agency is proposing a Category II classification for all combinations containing an expectorant and an oral antitussive if the antitussive is also an antihistamine. The agency is revising proposed § 341.40(g) and (i) to replace the phrase 'Any single oral antitussive active ingredient identified in § 341.14(a) * with the phrase "Any single oral antitussive active ingredient identified in § 341.14(a)(1) through (a)(4) * * *. This revision specifically excludes combinations containing diphenhydramine citrate or diphenhydramine hydrochloride as an antitussive.

(b) Combination drug products containing an anesthetic/analgesic and/ or a demulcent (in a solid dosage form) and an oral antitussive that is also an antihistamine. The Cough-Cold Panel reviewed data relating to combination drug products containing cough-cold and oral health care active ingredients with claims for relief of sore throat (41 FR 38312 at 38325). The Panel established specific criteria for the treatment of symptoms with combination products and based its Category I recommendations on whether the combination is rational concurrent therapy for a significant and existing population. The Panel determined that products containing an antitussive or a nasal decongestant combined with an oral anesthetic/analgesic in a lozenge dosage form are rational and

recommended a Category I classification for these combinations. The agency concurred with the Panel in the tentative final monograph for OTC cough-cold combination drug products. However, the agency determined that such a combination could be rational only if the combination drug product were in a solid dosage form so that the anesthetic/analgesic ingredient or the demulcent ingredient may exert its topical effect and the antitussive can be ingested (53 FR 30522 at 30536 and 30537).

The Panel did not discuss combinations containing an antihistamine with an anesthetic/ analgesic or a demulcent. However, the agency considered such combinations in the OTC cough-cold combinations tentative final monograph (53 FR 30522 at 30537). The agency stated that the combination of an antihistamine and an oral anesthetic/analgesic or an oral demulcent could be rational if the combination drug product is in a solid dosage form. In addition, the symptoms of allergic rhinitis and minor throat irritation that may result from the nasal congestion that often occurs with allergic rhinitis and subsequent breathing through the mouth could be treated concurrently with such combinations. However, the agency also stated that it was unaware of any currently marketed drug product that contains such a combination and that no data were submitted to demonstrate a significant target population with concurrent symptoms that would benefit from such a combination. Therefore, the agency proposed a Category III classification for the combination of an antihistamine with an oral anesthetic/analgesic or an oral demulcent. The agency has since determined that data do exist to support a target population for such combinations based on epidemiological data accepted by the Panel (41 FR 38312 at 38325). The agency believes that a Category I classification is appropriate for combinations containing an oral antitussive (which is also an antihistamine, although antihistamine claims cannot be made for these combinations) with an oral anesthetic/ analgesic or an oral demulcent if in a solid dosage form. Thus, the agency is proposing to include diphenhydramine citrate and diphenhydramine hydrochloride in combinations specified in § 341.40(j), (q), (u), (w), (x), and (z). At this time, sufficient data have not been provided to support a suitable target population with concurrent symptoms of sufficient duration to justify an antihistamine

claim for any of these combination drug products. Therefore, any of these combinations that contain diphenhydramine citrate or diphenhydramine hydrochloride as the antitussive cannot also make antihistamine claims. 2. Category II and III Combinations Containing an Antitussive.

The agency has considered all OTC cough-cold combinations containing an oral antitussive, but no antihistamine, that were placed in Category II or III in the OTC cough-cold combinations tentative final monograph (combinations in Table 1 under A.1. through A.18.). The agency has determined that these combinations would be categorized in the same manner if diphenhydramine were used as the antitussive. The agency is not aware of any data or information that would support reclassification of any of these combinations because they contain diphenhydramine rather than any other monograph oral antitussive ingredient.

3. Combinations Containing an Antihistamine With no Corresponding Category I Antitussive Combination.

The agency considered all antihistamine combinations (not including an oral antitussive) that did not have a corresponding Category I antitussive combination (not including an antihistamine), e.g., an antihistamine and an anticholinergic. The agency is not changing the classification of any of these combinations because they do not contain an antitussive component. Thus, these combinations are not pertinent to combinations that include an antitussive that is also an antihistamine.

B. OTC cough-cold combinations containing: (1) An oral antitussive and an antihistamine if the antitussive is also a antihistamine or (2) an antihistamine and an oral antitussive if the antihistamine is also an antitussive.

The Panel recommended a Category II classification for combinations containing: (1) An oral antitussive and an antihistamine if the antitussive is also a Category I antihistamine, and (2) an antihistamine and an oral antitussive if the antihistamine is also a Category I antitussive (41 FR 38312 at 38326). Such combinations include diphenhydramine and dextromethorphan or diphenhydramine and chlorpheniramine. The Panel stated that the combinations are not safe because the side effects of two drugs having the same action may combine. For example, the drowsiness effect of each ingredient may be additive and result in an unacceptable level of