

§ 348.50(b) (21 CFR 348.50(b)) (55 FR 6932 at 6951). However, data are lacking to support any combination drug products containing hydrocortisone with other OTC drug active ingredients. Further, the 1990 TFM cited by the requester did not include the term "swelling" as an acceptable claim.

(Comment 2) Pramoxine HCl is a Category I ingredient, and thus FDA considers it safe and effective for OTC use. The ingredient is included in § 346.10(g) (21 CFR 346.10(g)) of the OTC anorectal drug products FM for the treatment of various anorectal conditions, including pain, burning, itching, discomfort, and/or irritation. The requester contended that OTC anorectal drug products containing pramoxine HCl in the established dosages of 0.5 to 1 percent that are indicated to relieve pruritus ani may be lawfully marketed in accordance with the OTC anorectal drug products FM.

(Agency response) Pramoxine HCl 0.5 to 1 percent is a proposed Category I ingredient as a local anesthetic in the TFM for OTC external analgesic drug products (48 FR 5852 at 5867). The requester mentioned that this concentration range could be used in OTC anorectal drug products. However, only a 1 percent concentration is included in § 346.10(g) of the OTC anorectal drug products monograph as this was the only concentration evaluated in that rulemaking. The agency lacks data to support a lower concentration for external anorectal use.

(Comment 3) The agency has the authority to switch the status of a product from prescription to OTC when the active ingredient or the combination of active ingredients is determined to be safe and effective for OTC use. The requester cited the **Federal Register** of August 4, 1976 (41 FR 32580) and May 11, 1972 (37 FR 9464 at 9470) as sources for that authority.

(Agency response) The agency has made the determination that the combination of hydrocortisone and pramoxine HCl is not safe and effective for OTC use. Therefore, switching the status of the product from prescription to OTC is not an option. Although the agency is not bound by the recommendations of its advisory panels, the panels that reviewed these ingredients did not recognize any combination of "amine" and "caine" type local anesthetics with hydrocortisone preparations as safe and effective. The requester has also failed to provide adequate information to support a determination that the combination is safe and effective. The agency lacks sufficient data from available sources to propose a

combination of hydrocortisone and pramoxine HCl for OTC use in the applicable OTC drug rulemakings.

(Comment 4) Combination products containing hydrocortisone and pramoxine HCl should have been reconsidered by the agency when it extended the concentration range for hydrocortisone up to 1 percent. Specifically, the agency has the obligation to reconsider combination products when it determines that all of the active ingredients contained in the combination are Category I, and an interested person has requested the combination be considered under a particular OTC drug rulemaking proceeding (21 CFR § 330.10(a)(7) and (a)(12)) (21 CFR 330.10(a)(7) and (a)(12)).

(Agency response) The agency disagrees. The agency's proposal to increase the maximum concentration of hydrocortisone from 0.5 to 1 percent occurred in the rulemaking for OTC external analgesic drug products based on data on the single ingredient and not on combination products. There were no proposed hydrocortisone combinations in that rulemaking. The data on the combination of hydrocortisone 1 percent and pramoxine HCl were submitted to the rulemaking on OTC anorectal drug products and had not been reviewed by the agency at the time it published the amendment to the OTC external analgesic TFM on February 27, 1990 (55 FR 6932) extending the strength of hydrocortisone up to 1 percent. The agency published the FM on OTC anorectal drug products on August 3, 1990 (55 FR 31776 at 31777), in which it stated that hydrocortisone combinations were under review and the agency's evaluation would be reported separately in the future. Simultaneous publication of the agency's evaluation of the single ingredient hydrocortisone in the rulemaking for OTC external analgesic drug products and hydrocortisone-pramoxine HCl combinations in the rulemaking for OTC anorectal drug products would have delayed publication of the anorectal FM for several years.

(Comment 5) Prior to completing the FM for OTC external analgesic drug products, the agency should conduct a retrospective analysis of previously reviewed (or "should have been reviewed") hydrocortisone combinations marketed before 1979.

(Agency response) The agency previously reviewed combination drug products containing hydrocortisone and pramoxine HCl submitted during the 1970s and 1980s. In a notice of proposal

to withdraw approval of abbreviated new drug applications for fixed combination drug products containing hydrocortisone acetate and pramoxine HCl, the agency found no evidence that pramoxine HCl contributed an effect to the combination drug product (53 FR 25013, July 1, 1988).

(Comment 6) The agency has consistently applied its combination policy, except with respect to a hydrocortisone and pramoxine HCl combination. The agency did not require additional data in support of the effectiveness of combinations in the monographs for OTC antacid (simethicone and an antacid), cough-cold (ingredients from different pharmacological groups), laxative (bulk and stimulant laxatives), and anorectal drug products (not requiring final formulation testing of combination products and accepting the combinations as formulated).

(Agency response) The agency has consistently focused on the safety and effectiveness of each active ingredient, the rationale for concurrent therapy, the contribution each ingredient makes to the combination, and the marketing history to support Category I classification of combinations. Marketing history for the products cited by the requester provided more extensive data than were available for a combination of hydrocortisone and pramoxine HCl for anorectal use. There was an extensive marketing history for combinations of an antacid and simethicone, an antifoaming agent, ingredients with different indications. The agency required additional data for a number of cough-cold combinations in the TFM for those products (53 FR 30522, August 12, 1988). The combinations in the laxative TFM (50 FR 2124 at 2152 and 2153, January 15, 1985) and anorectal FM involve ingredients with the same indication. The Advisory Review Panel for OTC Laxative Drug Products (Laxative Panel) looked at laxative combinations and determined that each active ingredient had to make a contribution toward laxation. The Laxative Panel recommended monograph status only for combinations it determined had sufficient data. FDA agreed with the Panel's recommendation, and the agency has requested additional data to support other laxative combinations. The Hemorrhoidal Panel evaluated and recommended combinations of anorectal ingredients (45 FR 35576 at 35673), but did not evaluate hydrocortisone because information on that ingredient was not submitted for its review. The Advisory Review Panel on OTC Topical Analgesic, Antirheumatic,