

Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) discussed combinations of external analgesic ingredients, including hydrocortisone and pramoxine HCl, but did not recommend this combination for monograph status (44 FR 69768 at 69790, December 4, 1979).

The agency has not always accepted a panel's recommendation that specific combinations should be allowed, without having adequate supporting data. For example, the Advisory Review Panel on OTC Antimicrobial (II) Drug Products recommended monograph status for combinations of up to three antifungal ingredients and hydrocortisone or hydrocortisone acetate 0.5 to 1 percent (47 FR 12480, March 23, 1982). The agency disagreed with that panel's recommendations because the agency found that these combinations lacked adequate evidence of effectiveness (47 FR 12480 at 12481). The rulemaking for antifungal drug products has been completed and, because adequate data were not provided to support this combination, it remains nonmonograph. No combination containing hydrocortisone has been found to be generally recognized as safe and effective for OTC use. Thus, the agency is consistent in requiring additional data to support this hydrocortisone-pramoxine HCl combination.

(Comment 7) Currently marketed prescription products containing 1 percent or less hydrocortisone and 1 percent pramoxine HCl meet the combination policy implemented by the agency. The OTC drug combination policy standards are satisfied because the active ingredients are Category I, are present in the established dosage range, and each ingredient represents a different therapeutic category. The requester also mentioned a previously submitted clinical protocol (Ref. 3) that was not initiated because this protocol was suspended following a meeting with FDA (Ref. 4).

(Agency response) The agency's requirements for OTC drug combination products in § 330.10(a)(4)(iv) also include that each active ingredient makes a contribution to the product's claimed effect(s). The agency has no data showing that the combination of hydrocortisone and pramoxine HCl has been clinically tested against each individual active ingredient and a placebo. As the agency discussed in its January 13, 1994, letter to the requester (Ref. 2), the submitted data did not include these types of studies. Further, the studies from the literature did not involve a patient population where the

product is intended for OTC use, nor were they for the proposed OTC anorectal indication. Therefore, based on the available data, the agency is unable to conclude that each active ingredient makes a contribution to the product's claimed effect(s) and that this combination is generally recognized as safe and effective. After the agency received a letter indicating that the requester's client had suspended an ongoing study of the combination (Ref. 4), the agency was under the impression that there was no longer interest in having the protocol reviewed. The requester should notify the agency if there is still interest in conducting the appropriate study and having the protocol reviewed.

(Comment 8) The combination of 1 percent or less hydrocortisone and 1 percent pramoxine HCl is warranted because hydrocortisone is a therapeutic equivalent of other active antipruritic ingredients that may be combined with a local anesthetic such as pramoxine HCl. In the past, the agency has permitted active ingredient substitutions with pharmacological classes. Further, while the method of action of hydrocortisone is different than other antipruritic agents, the requester suggests that it can be properly combined with local anesthetics, because it is therapeutically equivalent, if not superior, to other approved antipruritic agents.

(Agency response) The agency's response under section II, comment 6 of this document applies here also. The requester's belief that the combination of an antipruritic/analgesic with a local anesthetic is permitted by implication is incorrect. Section 346.22 (21 CFR 346.22) provides for the combination of an "antipruritic/analgesic and a local anesthetic with an astringent." The ingredients under proposed § 348.10 (48 FR 5852 at 5868) are classified as "analgesic/anesthetic/antipruritic."

Listed combinations of external analgesic active ingredients under proposed § 348.50 include ingredients listed under § 348.10(a), (b), and (c) exclude hydrocortisone preparations which are listed under proposed § 348.10(d)(1) as hydrocortisone and under (d)(2) as hydrocortisone acetate. The Topical Analgesic Panel classified hydrocortisone preparations in a listing of ingredients that depress cutaneous sensory receptors (analgesics, anesthetics, and antipruritics) (44 FR 69768 at 69865, December 4, 1979). The agency subdivided the analgesic, anesthetic antipruritic ingredients into separate classes, i.e., "caine" type local anesthetics, alcohols and ketones, antihistamines, and hydrocortisone

preparations (48 FR 5852 at 5867 and 5868, February 8, 1983). The Topical Analgesic Panel did not have adequate data to consider hydrocortisone and pramoxine HCl interchangeable, and the agency has no basis to recommend their interchangeability and inclusion in any OTC drug product monograph.

(Comment 9) If the agency is unable to conclude from the information presented that the proposed combination is Category I, the agency should grant a hearing in this matter.

(Agency response) The agency has evaluated all of the evidence in support of a combination of hydrocortisone and pramoxine HCl in the administrative record for the rulemaking for OTC anorectal drug products submitted on behalf of the requester's client. The agency has discussed this information in its letter of January 13, 1994 (Ref. 2) and in this document. The agency does not find an oral hearing warranted.

III. Analysis of Impacts

FDA has examined the impacts of this final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts, and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation). The final rule that led to the development of this supplemental final rule was published in 1990, before the Unfunded Mandates Reform Act of 1995 was enacted. The agency explains in this final rule that the final rule will not result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million.

The agency concludes that this final rule is consistent with the principles set out in the Executive order and in these two statutes. The final rule is not a