DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310, 346, and 369

[Docket No. 80N-0050]

Anorectal Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) anorectal drug products for the relief of symptoms associated with hemorrhoids and other anorectal disorders are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Hemorrhoidal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by December 13, 1988. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 120 days for comments and objections instead of the normal 60 days. New data by August 15, 1989. Comments on the new data by October 15, 1989. Written comments on the agency's economic impact determination by December 13, 1988.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 27, 1980 (45 FR 35576), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC anorectal drug products, together with the recommendations of the Advisory Review Panel on OTC Hemorrhoidal Drug Products (Hemorrhoidal Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by August 25, 1980. Reply comments in response to comments filed in the initial comment period could be submitted by September 24, 1980.

In a notice published in the **Federal Register** of September 26, 1980 (45 FR 63876), the agency advised that it had reopened the administrative record for OTC anorectal drug products to allow for consideration of recommendations on camphor-containing drug products that had been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) after the date the administrative record previously had officially closed. The agency concluded that the Miscellaneous External Panel's recommendations should be available to the agency in developing a proposed regulation on anorectal drug products in the form of a tentative final monograph. (See comment 21 below.)

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking, nine drug manufacturers, one drug manufacturers' association, six health professionals, and one consumer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on May 27, 1980 (45 FR 35576), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 346 (21 CFR Part 346), FDA states for the first time its position on the establishment of a monograph for OTC anorectal drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC anorectal drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC anorectal drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summaries of the comments and FDA's responses to them.

In the **Federal Register** of February 8, 1983, the agency published a tentative final monograph for OTC external analgesic drug products which included a labeling claim "for external anal itching" for hydrocortisone-containing products. After reviewing and evaluating that tentative final monograph and in response to a comment submitted to the anorectal rulemaking, the agency has decided to retain the above labeling claim and hydrocortisone in the external analgesic rulemaking rather than include them in the anorectal rulemaking. In this way, the various conditions for which hydrocortisone is effective will be listed in one monograph. In a future issue of the **Federal Register**, the agency will amend the tentative final monograph for OTC external analgesic drug products to include a requirement that hydrocortisone-containing products labeled for "anal itching" also be labeled with appropriate general warnings and directions consistent with other OTC anorectal drug products. (See comment 25 below.)

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required)

at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC anorectal drug products (published in the **Federal Register** of May 27, 1980; 45 FR 35576), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of whether further testing was undertaken to justify their future use. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 30 days after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of April 26, 1973 (38 FR 10307) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch (address above).

I. The Agency's Tentative Conclusions on the Comments

A. General Comments on Anorectal Drug Products

1. Two comments expressed their continuing position that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comments referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).

2. Several comments pointed out that a number of the Panel's recommendations do not represent the unanimous opinion of the Panel members because the Panel was divided four to three on many issues. Some of the comments argued that the minority view often demonstrated a greater clinical understanding than the majority view. The comments urged FDA, when evaluating the Panel's recommendations, to consider the minority view and the fact that there was not a clear consensus of the Panel.

Other comments contended that the Panel did not apply the same standards in classifying the various active ingredients, arguing that pramoxine was placed in Category I on the basis of old and questionable data, while live yeast cell derivative was placed in Category III despite objective data that were endorsed by experts. The comments requested that the agency carefully review all of the Panel's recommendations to determine if the Panel took an equitable approach in its evaluation of all ingredients contained in hemorrhoidal drug products.

In evaluating the Panel's recommendations, the agency has considered the comments' criticisms, reviewed the data submitted to the Panel, considered the minority's views, reviewed the current scientific literature, and evaluated new data submitted since the Panel's report was published. The agency's proposals in this tentative final monograph are based on consideration of all of these factors. (See comments 14 and 23 below for specific discussions of pramoxine and live yeast cell derivative.)

3. One comment requested that the agency include all available transcripts of the Panel's meetings in the administrative record.

The agency does not ordinarily include transcripts of panel meetings in the administrative record. The reasons for this are stated in the preamble to the "Proposal to Designate the Contents and the Time of Closing of the

Administrative Record," published in the **Federal Register** of June 4, 1974 (39 FR 19878). (The final rule was published in the **Federal Register** of November 8, 1974 (39 FR 39556).) Any comments relating to transcripts of panel meetings should state the reasons that would warrant the agency's consideration of the transcripts or particular portions of the transcripts, notwithstanding the reasons given by the agency for not ordinarily considering them. The comment did not state any reasons; therefore, the agency is not including the transcripts of the Panel's meetings in the administrative record.

4. Murray Berdick, Ph. D., commented that his name was omitted from the list of individuals who appeared before the Panel (45 FR 35577). He stated that his presentation is included in the transcript of the Panel's April 29, 1977 meeting and is cited as reference 12 at 45 FR 35627. He also indicated that his name was incorrectly spelled at 45 FR 35635, column 2, reference 6.

The agency regrets that Dr. Berdick's name was omitted from the list of persons who appeared before the Panel and was incorrectly spelled in the cited reference at 45 FR 35635.

5. One comment stated that the Thornton and Minor Clinic and Hospital and the McCleary Hospital of Kansas City, Missouri, were not mentioned in the Panel's overview of the history of anorectal diseases and their treatment (45 FR 35581). The comment added that the Clinic specializes in the research and treatment of anorectal disorders and included an account of its history.

The agency appreciates the comment's pointing out these omissions from the Panel's report. However, the historical discussion of anorectal diseases and their treatment was included as background in the Panel's report and was not intended to be all-inclusive.

6. One comment pointed out that the correct citation at 45 FR 35627 for data submitted in support of the barrier effect of protectants should have been Reference 9, OTC Volume 120052, not Reference 6, which is "Remington's Practice of Pharmacy." Another comment stated that a protocol for a product containing dibucaine apparently was erroneously attributed to Ciba-Geigy in the administrative record and that this firm did not submit this protocol.

The agency acknowledges that Reference 6 at 45 FR 35627 should have been identified as OTC Volume 120052. The protocol erroneously attributed to Ciba-Geigy should have been attributed to Myer Laboratories.

7. One comment argued that publication of a call-for-data notice in the **Federal Register** amounted to inadequate notice to manufacturers of hemorrhoidal drug products and discriminated against the smaller manufacturer or packager who, with only a small support staff, may not have the resources to employ an individual to read the **Federal Register** every day. The comment stated that its marketed hemorrhoidal preparation containing ephedrine alkaloid and 8-hydroxyquinoline was not submitted to the Panel for review because of this lack of notice. Consequently, these ingredients were not reviewed by the Panel and would become Category II in a final rule. The comment objected to such a Category II classification for these ingredients, adding that the rectal preparation in which they are combined has been used successfully for over 20 years.

In addition to the call-for-data notice (38 FR 10307), the agency regularly published notices in the **Federal Register** announcing the dates of the Panel's meetings and the part of each meeting that was open to the public. The minutes of each meeting were made publicly available, and the industry liaisons, who served on the Hemorrhoidal Panel as nonvoting members, were nominated by The Proprietary Association, the national trade association of OTC drug manufacturers. In addition, the OTC drug review has been highly publicized, and the Panel's review of anorectal drug products covered a period of over 4 years.

For these reasons, the agency believes that adequate opportunity was provided for all parties to present their positions to the Panel. Ample opportunities have existed and continue to exist for all interested persons to express their opinions before publication of the final rule. For example, interested persons could have submitted comments and data during the comment period following publication of the Panel's report and may do so again following publication of the tentative final monograph. (See § 330.10(a) (6) and (7).)

The comment did not submit any data to support the safety and effectiveness of ephedrine alkaloid or 8-hydroxyquinoline used in anorectal drug products. Therefore, the agency has no basis for classifying these ingredients in this tentative final monograph. As stated above, additional data may be submitted for 12 months following publication of this tentative final monograph.

8. One comment contended that the Panel failed to evaluate or discuss two clinical studies submitted to show that its proposed product (an aerosol medicated anal wipe foam) was significantly effective for relief of pain and itching in persons with anorectal disease (Refs. 1 and 2). Referring to the statement at 45 FR 35590 that "the need to produce a foam for delivering the active ingredient is not clear to the Panel," the comment contended that the Panel failed to perceive that all foams are not "shaving lather-type" foams. The comment stated that its anhydrous foam is a "quick-breaking" type of foam and serves only as a delivery vehicle. As the foam is applied to the toilet tissue it breaks and leaves a local anesthetic suspension, while the emollients and other ingredients are left in solution for skin application.

Although not referred to in the Panel's general statement on foams, the data submitted by the comment were reviewed by the Panel and referred to in the discussion of testing guidelines at 43 FR 35595. The Panel also discussed the use of foam products for delivering an active ingredient externally in the anal canal and in the lower rectum below the dentate line (43 FR 35589 and 35590). Because the agency is not proposing the Panel's requirement for final formulation testing in this tentative final monograph, Category I anorectal ingredients can be formulated in any dosage form for external use, including foams, provided the product meets each condition of the final monograph. (See comment 55 below.)

However, the proposed product to which the comment referred would have anesthetic, counterirritant, emollient, and/or antipruritic properties (Ref. 1). The Panel concluded that it is not rational to combine a local anesthetic and a counterirritant and placed such combinations in Category II.

The agency concurs. Thus, the comment's proposed product would be considered a Category II combination. (See comment 34 below.)

References

(1) OTC Volume 120035.
(2) OTC Volume 120037.

B. Comments on Local Anesthetics

9. One comment supported the opinion of the Panel minority that local anesthetics in anorectal drug products should be Category I for intrarectal use instead of Category III, as recommended by the Panel majority. The comment cited the minority's reasoning that, even without double-blind studies, the effectiveness of local anesthetic-containing anorectal drug products that are used intrarectally is supported by marketing records of repeat sales, use

experience, and Panel members' clinical experience with patients who claimed relief of discomfort after intrarectal use of these products.

The agency has thoroughly considered the issue of intrarectal (internal) use of local anesthetics and finds that, at present, there is insufficient evidence of general recognition of the safety and effectiveness of this use of local anesthetics. The lack of general recognition is demonstrated by the fact that the Panel was not unanimous in its recommendations.

The Panel majority pointed out that there are no known sensory pain fibers above the dentate line (45 FR 35607). Hence, the majority concluded that there is insufficient evidence to prove that local anesthetics used intrarectally are effective. In addition, the Panel majority felt that local anesthetics can easily diffuse through mucous membranes and, when applied intrarectally can be absorbed directly into the systemic, central, and portal blood circulations almost as rapidly, under certain conditions, as intravenous administration. Thus, these drugs raise potential safety questions and could cause severe reactions in certain individuals.

After reviewing the available scientific evidence, the Panel concluded that certain local anesthetics, i.e., benzocaine, benzyl alcohol, dyclonine, and pramoxine, could be used safely intrarectally but that data were still needed to establish effectiveness. (See 45 FR 35613 to 35619.)

The Panel minority believed that the majority based its conclusion on the fact that there are no anatomically identifiable sensory nerve endings or nerve fibers in the rectal mucosa or submucosa. However, the minority argued that there are known and identifiable nerve fibers and plexuses between the muscular layers that are associated with peristaltic muscular contraction of the rectum. The minority concluded that these nerve fibers, which are known to innervate the smooth musculature of the rectum, have synapses with cells in the myenteric and submucosal plexuses. In addition, the fibers have or are in adjacent association with sensory conducting nerve fibers, which transmit impulses to the central nervous system.

The minority argued that, although electrical stimulation or application of a mustard suspension to the rectal mucosa has not been shown to evoke a pain response in healthy mucosa, pain perception may result when blood vessels supplied with sensory pain fibers become diseased with hemorrhoids. However, evidence based on well-controlled clinical studies is lacking to support this argument. In addition, both the majority and minority of the Panel discussed the fact that some sensation of pressure can be produced in the rectum by distention due to feces or gas (45 FR 35607 to 35608). The agency is not aware of evidence that the source or sources of this sensation are also capable of transmitting the sensations of pain or itching.

Finally, in support of intrarectal use of local anesthetics, both the comment and the Panel minority cited marketing records of repeat sales of products containing local anesthetics for intrarectal use. They also cited use experience, particularly that of Panel members' patients who claimed relief of anorectal discomfort after use of these products. The agency recognizes that proof of effectiveness may not always consist of controlled clinical investigations. In fact, the OTC drug review regulations in 21 CFR 330.10(a)(4)(ii) provide that investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. However, after carefully reviewing all the available literature, the agency agrees with the Panel majority (45 FR 35607) that the intrarectal effectiveness of all local anesthetics remains unsubstantiated and requires further study. (See also comment 11 below.) However, the agency emphasizes that this decision does not affect the external use of these ingredients. OTC anorectal anesthetics are being included in the tentative final monograph with appropriate labeling for external use only.

The agency invites public comment and submission of data on the safety and effectiveness of OTC anorectal anesthetic drugs for intrarectal use. Pending receipt and review of such data and information, the agency proposes that the intrarectal use of OTC anorectal anesthetic ingredients be considered a Category III condition except for those ingredients or conditions that are proposed as Category II.

10. One comment stated that the Panel's recommended monograph refers to dibucaine base and dibucaine hydrochloride, but that only dibucaine base is presently available in formulations intended for anorectal use.

In addition to the data submitted on dibucaine base, the Panel chose to review the hydrochloride salt, noting that the base is slightly water soluble and moderately lipid soluble, whereas the hydrochloride salt is soluble in water and in organic solvents (45 FR 35614). The Panel considered dibucaine base and dibucaine hydrochloride as pharmacologically equivalent, and the agency concurs. Dibucaine base and dibucaine hydrochloride were classified by the Panel as Category III for external and intrarectal use (45 FR 35614) and therefore were not included in the Panel's recommended monograph. However, as discussed in comment 12 below, the agency is proposing Category I status in this tentative final monograph for dibucaine base and dibucaine hydrochloride for external use. Intrarectal use of these ingredients is Category III. (See comment 9 above and comment 11 below.)

11. One comment submitted summaries of six studies (Ref. 1) and requested that dibucaine be classified Category I as a local anesthetic for intrarectal use. Noting that these same summaries had been submitted to the Panel (Ref. 2), the comment stated that the Panel apparently found the results presented in these summaries to be insufficient to demonstrate the effectiveness of dibucaine for intrarectal use. The comment added that, although the data generated by these studies do not demonstrate statistical significance in all parameters, it believes that dibucaine has been shown in the clinical practice setting to be effective in the relief of hemorrhoidal symptoms. The comment pointed out that the studies had been reviewed by other authorities who found that the studies, as a whole, demonstrate the effectiveness of dibucaine used intrarectally (Refs. 3 and 4). The comment subsequently submitted additional effectiveness data (Ref. 5).

In addition, the comment disputed the Panel's conclusion that dibucaine had not been shown to be safe for intrarectal use because of possible systemic toxicity when administered intrarectally. Contending that further safety data are not needed, the comment stated that studies in which dogs and monkeys were administered high doses of dibucaine intrarectally did not show serum levels as high as those of dibucaine administered intravenously. The comment added that lipid vehicles retard the rate and extent of absorption of local anesthetics, that marketing history and submitted studies attest to dibucaine's safety when used intrarectally, and that further testing of humans using high doses of dibucaine would be unethical.

The agency has evaluated the summaries submitted by the comment (Ref. 2) and the additional effectiveness data (Ref. 5). The same summaries were submitted to the Panel on April 27, 1977

(Ref. 2). Other data and information on these studies including the opinions of the other authorities mentioned by the comment had also been submitted to the Panel on June 22, 1973 (Ref. 4) and on July 29, 1974 (Ref. 3). The Panel reviewed all of these data, plus other data, and concluded that the effectiveness of local anesthetics, including dibucaine, for intrarectal use is unproven (45 FR 35616). The agency concurs with that determination.

The additional effectiveness data involved a randomized, double-blind comparison in 143 patients of an ointment containing dibucaine base and the ointment base minus dibucaine for relief of pain, burning, and/or itching associated with internal, external, or mixed hemorrhoids (Ref. 5). (The summary of this study had been reviewed by the Panel (Ref. 2).) Only 127 cases were suitable for analysis; 65 patients received the ointment containing dibucaine base while 62 patients received the ointment base without dibucaine. Despite several problems in evaluation, including heterogeneous disease processes of external hemorrhoids, internal hemorrhoids, and mixed hemorrhoids, and variable patient medication compliance, and despite probable contribution from the ointment vehicle base, the ointment containing dibucaine base was shown in this study to be superior to the ointment base in seven of the measurements for which there was significance at the 5-percent level or greater; this leaves two measurements where the ointment base was judged superior at the same level of significance.

Only 15 patients who received the ointment containing dibucaine base and 14 patients who received the vehicle alone had internal hemorrhoids. The rest of the patients had either external hemorrhoids or mixed hemorrhoids (50 patients who received the ointment containing dibucaine base and 48 patients who received the vehicle control).

In about 75 percent of the cases there were external complaints (external to the dentate line) and in about 25 percent of the cases complaints were judged to be as a result of internal hemorrhoids. However, the data are analyzed only for the entire group, with no analysis exclusively for those patients with internal hemorrhoids. Further, the agency believes such an analysis would not be meaningful because it would involve 29 patients derived from 9 investigators or about 3 cases per investigator.

There are insufficient data to establish that the ointment containing dibucaine base is effective for the relief of pain, burning, discomfort, and itching associated with internal hemorrhoids. The safety of internal application also has to be established for dibucaine base. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 6).

References

(1) Comment No. C00008, Docket No. 80N-0050, Dockets Management Branch.
(2) OTC Volume 120064.
(3) OTC Volume 120023.
(4) OTC Volume 120010.
(5) Comment No. SUP002, Docket No. 80N-0050, Dockets Management Branch.
(6) Letter from W. E. Gilbertson, FDA, to R. Gauch, Ciba-Geigy Corp., coded LET011, Dockets Management Branch.

12. Disputing the Panel's statement at 45 FR 35616 that "there are no studies using dibucaine in the perianal area," one comment cited data on a controlled study that had been submitted to the Panel. The study involved approximately 45 patients with external hemorrhoids and 65 patients with both internal and external hemorrhoids (Ref. 1). The comment argued that the Panel placed pramoxine in Category I for external use based on data from two uncontrolled studies and placed benzocaine in Category I for external use based on one unblinded, nonrandomized study that used only 13 patients. The comment stated that the Panel either used different standards in determining the effectiveness of dibucaine than it used for pramoxine and benzocaine or discounted or ignored the "superior" data submitted for dibucaine.

Contending that proof of dibucaine's effectiveness as a local anesthetic need not relate solely to its use in the perianal area, the comment pointed out that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) classified dibucaine in Category I for external use for "the temporary relief of pain and itching due to * * * minor cuts, abrasions * * *, and minor skin irritations." The comment added that the Hemorrhoidal Panel stated that dibucaine is probably effective on abraded skin of the perianal area, and that the Topical Analgesic Panel found dibucaine to be effective on abraded skin generally. The comment further contended that abraded skin is abraded skin regardless of its location and that there is no justification for categorizing dibucaine as anything less than Category I for use on perianal skin. The comment urged the agency to consider the fact that many patients over the years have obtained relief using dibucaine and that, for all of the above reasons, a Category I classification of dibucaine as a local anesthetic for external use in anorectal disease is warranted.

Although the comment requested Category I status specifically for dibucaine, the agency notes that the Panel considered dibucaine (base) and dibucaine hydrochloride to be pharmacologically equivalent (see comment 10 above); therefore, this discussion on external use applies to both ingredients. (The intrarectal use of local anesthetics is discussed in comment 9 above.)

The Panel reviewed the data referred to by the comment and applied the same standards in reaching its conclusions on benzocaine, dibucaine, dibucaine hydrochloride, and pramoxine hydrochloride (45 FR 35609 to 35610 and 35614 to 35617), namely that the effectiveness of an OTC anorectal active ingredient should be demonstrated in the vehicle in which it would be marketed and that the final formulation should be tested in the anorectal area. The Panel concluded that adequate data were submitted to permit classification of benzocaine and pramoxine hydrochloride in specific vehicles in Category I for external use. However, although the data submitted to the Panel contained studies using final formulations of dibucaine, the Panel concluded that because of the lack of studies on perianal skin the data were not sufficient to establish the effectiveness of dibucaine for external use for relieving anorectal conditions (45 FR 35616).

In the tentative final monograph for OTC external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5852), the agency tentatively adopted the recommendations of the Topical Analgesic Panel and proposed that dibucaine and dibucaine hydrochloride in concentrations of 0.25 to 1 percent be generally recognized as safe and effective for external use. Having reviewed both Panels' recommendations, the agency believes that the data on dibucaine and dibucaine hydrochloride show that these ingredients when applied to the skin of the perianal area and anal canal are as safe and effective as when used on the skin of other areas of the body. Therefore, in this tentative final monograph the agency is proposing dibucaine and dibucaine hydrochloride as Category I for external use.

The agency notes that the Hemorrhoidal Panel's recommended

dosage range for dibucaine and dibucaine hydrochloride was 2.5 milligrams (mg) to 20 mg per dosage unit. The minimum effective dose of 2.5 mg per dosage unit was based on the amount of dibucaine in a marketed suppository for intrarectal use, for which data were submitted to the Panel. The maximum safe dose of 20 mg per dosage unit was based on the amount of the ingredient contained in a 2-gram (g) dose of a 1-percent ointment for external and intrarectal use, for which data were also submitted to the Panel. The agency notes that the 2.5-mg suppository dosage form is no longer marketed and is unaware of any other currently marketed product that contains 2.5 mg dibucaine per dosage unit. The 1-percent ointment is still marketed. Therefore, the agency is proposing that the dosage of dibucaine and dibucaine hydrochloride for external use be expressed in a concentration range of 0.25 to 1 percent for use up to 3 or 4 times daily, which is consistent with the tentative final monograph for OTC external analgesic drug products (48 FR 5852). In addition, because the agency did not propose any limitation on the maximum safe daily dose of this ingredient for topical use in the external analgesic tentative final monograph, and because the Panel's recommended limitation on the maximum daily dose of dibucaine was based on the potential safety concerns resulting from intrarectal application, the agency is not proposing the 80-mg maximum daily dose limitation recommended by the Hemorrhoidal Panel for dibucaine and dibucaine hydrochloride.

Reference

(1) OTC Volume 120064, pp. 6, 7, 10, 19–21, 31–33, and 50–57.

13. One comment supported the Panel's interim decision, made at its 7th and 16th meetings, to place diperodon (0.5 to 1 percent) in Category I for external use. The comment contended that the Panel's decision during its 28th meeting to place diperodon in Category III was based largely on double-blind studies showing that diperodon was only slighty more effective than placebo. The comment disputed the Panel's final recommendation to place diperodon in Category II for external use and cited a study to support the effectiveness of diperodon (Ref. 1). The comment also cited the **Federal Register** of June 18, 1971, in which the comment stated that FDA published the findings of the National Academy of Sciences-National Research Council's (NAS–NRC) Drug Efficacy Study Group that diperodon was possibly effective for the temporary relief of anorectal pain and itching, as well as for anesthetic and mild antiseptic action. The comment stated that safety is not at issue and contended that the difference in scientific opinion as to diperodon's effectiveness should not result in its placement in Category II.

During the course of the Panel's deliberations the classification of diperodon was tentative; however, with the publication of its recommendations in the **Federal Register**, the Panel's final classification of diperodon was as follows: Category II for external use and Category III for intrarectal use. Only the external use of diperodon is discussed in this response. The intrarectal use of local anesthetic ingredients is discussed elsewhere in this document. (See comment 9 above.)

After reviewing the data submitted to the Panel and the references cited by the comment, the agency concludes that diperodon can be reclassified from Category II to Category III for external anorectal use but that the data remain inadequate to reclassify it into Category I.

The published study (Ref. 1) and the June 18, 1971 **Federal Register** notice describing the NAS–NRC report, which were referenced by the comment, and an unpublished study in humans (Ref. 2) were evaluated and cited by the Panel in its discussion of the effectiveness of diperodon for external use (45 FR 35612). The Panel concluded that diperodon was not effective for OTC external anorectal use because the predominant results of the studies show no statistical difference between diperodon and placebo.

With respect to the published study (Ref. 1), although the investigators concluded that diperodon was effective as a topical anesthetic in this dermal abrasion study in the guinea pig, there is a lack of evidence that diperodon produces clinically significant topical anesthetic action in humans.

In the unpublished study, 43 patients were randomized to receive an ointment containing diperodon or placebo in double-blind fashion on the day following anorectal surgery (Ref. 2). The patients evaluated the degree of pain (none, mild, moderate, severe) on the morning of the first post-operative day just prior to application of the test product (baseline) and again at 10, 20, 40, and 60 minutes following ointment application. The agency has analyzed the pain score data and concludes that the response at 40 and 60 minutes favored the diperodon-containing ointment, although differences did not achieve statistical significance at the conventional 0.05 level.

Results of four other controlled studies of the ointment containing diperodon that were submitted to the Panel (Ref. 3) failed to confirm the positive results of the above unpublished study (Ref. 2). Two of these studies were similar in design to the unpublished study discussed above and involved more patients; however, all of these studies failed to show a significant drug effect. Without independent replication of the findings in the unpublished study (Ref. 2), it is difficult to draw definitive conclusions concerning the effectiveness of diperodon as a topical anesthetic.

Although the evidence of the effectiveness of diperodon as a local anesthetic is conflicting, some of the data are suggestive of effectiveness. Therefore, the agency is upgrading diperodon as a local anesthetic for external anorectal use from Category II to Category III. Additional data are needed before the effectiveness of diperodon for external anorectal use can be established. The agency's detailed comments and evaluation of the data are on file in the Dockets Management Branch (Ref. 4).

References

(1) Campbell, A.H. et al., "In Vivo Evaluation of Local Anesthetics Applied Topically," *Journal of Pharmaceutical Sciences*, 57:2045–2048, 1968.

(2) Lieberman, W., Protocol 039–WL–001, OTC Volume 120075.

(3) OTC Volume 120075.

(4) Letter from W.E. Gilbertson, FDA, to J.P. Tierney, Counsel for Thornton-Minor McCleary Ointment Co., coded LET009, Docket No. 80N–0050, Dockets Management Branch.

14. One comment requested that the Panel's recommendations in § 346.10(b) for a cream or jelly formulation for pramoxine hydrochloride be expanded to include ointments and aqueous vehicles. The comment stated that the rate-limiting step in drug absorption in the anorectal area is the rate of release of the dissolved drug from the melted base. With a salt such as pramoxine hydrochloride, the rate of release would be increased by using a lipid base because the salt would be released rapidly from lipid to water and be available for treating the affected area. This comment also stated that if the intrarectal use of local anesthetics is classified in Category III, the suppository dosage form of pramoxine hydrochloride should also be included in Category III.

Two comments requested that the monograph include an aerosol foam dosage form of pramoxine hydrochloride. Noting that the Panel

stated that the need for a foam anorectal dosage form was unclear, one of the comments argued that the agency established the need and rationale for this dosage form by approving as safe and effective two prescription anorectal drug products containing a steroid in an aerosol foam. The comment submitted data to show that the mucoadhesive properties of the aerosol foam product, discussed by the Panel at 45 FR 35590, provide a rapid and complete coverage of the rectal mucosa compared with the slow and incomplete coverage provided by a conventional suppository (Ref. 1).

The submissions on pramoxine hydrochloride presented to the Panel included information on various dosage forms (45 FR 35590, 35610, and 35611); however, only one submission for jelly and cream dosage forms contained complete information as to the content of the final formulation, i.e., inactive ingredients (Ref. 2). Because the Panel concluded that the final formulation of anorectal products must be tested for safety and effectiveness (45 FR 35588) and because the only data submitted which identified the complete final formulation were for a cream and a jelly (Ref. 2), it placed only those dosage forms and the specific ingredients contained in the marketed formulations in its recommended monograph. Nevertheless, after reviewing the submitted data for all dosage forms, including those which did not specifically identify the inactive ingredients in the final formulations, the Panel stated that no toxic effects were noted in the clinical use of pramoxine hydrochloride as an aerosol foam, in suppositories, and in other vehicles including ointments and solutions (45 FR 35610 and Ref. 3).

Regarding the use of an aerosol foam, the Panel stated that the need to produce a foam for delivering the active ingredient was not clear (45 FR 35590) and that a properly designed ointment applicator should serve the same purpose as a foam delivery system. However, the Panel also stated that it did not intend to restrict ingenuity in product design as long as the product accomplishes the claimed effect and met the same final formulation requirements of safety and effectiveness as any other dosage form. The agency is aware that topical aerosol foam products containing pramoxine hydrochloride 1 percent labeled for anorectal use have been marketed OTC for a number of years (Refs. 4 and 5). Accordingly, based on the safety of this ingredient for external anorectal use and the knowledge that an aerosol foam is an effective delivery system for external anorectal use, the agency finds a topical aerosol foam dosage form of pramoxine hydrochloride acceptable for OTC use. Likewise, based on the history of many anorectal drug products being marketed in ointment dosage forms and the data submitted to the Panel (Ref. 2), the agency believes that an ointment vehicle would be acceptable for pramoxine hydrochloride when used externally.

Suppositories containing pramoxine hydrochloride, however, would not be acceptable dosage forms at this time because of insufficient data to establish the effectiveness of local anesthetics when used intrarectally. (See comment 9 above.) There is a lack of experience with formulations of this drug and similar anorectal drugs in aqueous vehicles. The Panel stated that an aqueous solution of pramoxine hydrochloride is not useful in anorectal products because the ingredient will not remain at the site of action (45 FR 35611).

As discussed in comment 55 below, specific dosage forms or specific formulations for anorectal active ingredients are not identified in this tentative final monograph. Thus, in formulating anorectal drug products containing pramoxine hydrochloride, manufacturers should assure that the vehicle is safe and suitable for anorectal use and that the active ingredient will be properly released from the formulation.

References

(1) Comment No. C00015, Docket No. 80N–0050, Dockets Management Branch.
(2) OTC Volume 120084.
(3) OTC Volume 120015.
(4) OTC Volume 120039.
(5) OTC Volume 120050.

C. Comments on Vasoconstrictors

15. One comment questioned whether the Panel's Category I recommendation for ephedrine sulfate and phenylephrine hydrochloride "in aqueous solution" for external and intrarectal use could be interpreted to mean that the ingredients could be dissolved in the aqueous phase of either an oil-in-water or water-in-oil emulsion vehicle.

The data reviewed by the Panel primarily focused on aqueous solutions of ephedrine sulfate and phenylephrine hydrochloride (45 FR 35622 and 35624). Because of the Panel's concerns about the need for final formulation testing to support safety and effectiveness, the agency believes that the Panel felt that these ingredients had only been determined to be effective when present in an aqueous solution. The agency is not proposing the Panel's recommendation for final formulation testing, and therefore specific vehicles (e.g., oil-in-water or water-in-oil emulsions) for anorectal active ingredients are not being identified in this tentative final monograph. (See comment 55 below.) Thus, in formulating anorectal drug products containing ephedrine sulfate or phenylephrine hydrochloride, manufacturers should assure that the vehicle is appropriate for anorectal use and that the active ingredient will be properly released from the formulation. Manufacturers should be aware that the newness of a dosage, or method * * * of administration or application, or other condition of use * * * may affect the "newness" of a drug. (See 21 CFR 310.3(h)(5).)

16. One comment maintained that statements made by the Panel concerning formulations containing ephedrine sulfate are contradictory. The comment noted that the Panel stated at 45 FR 35587 that water-soluble, oil-insoluble salts, such as ephedrine sulfate, are preferred for rapid absorption from a fat-type base, such as cocoa butter, but that the Panel stated at 45 FR 35622 that ephedrine sulfate is Category I only in an aqueous solution.

In discussing the effectiveness of ephedrine sulfate, the Panel stated that incorporation of ephedrine sulfate in an ointment appears reasonable to provide better surface contact and greater effectiveness. However, the Panel noted that neither a literature survey nor a review of the submitted data provided effectiveness studies on the formulation of ephedrine sulfate in an ointment (45 FR 35623). The Panel recommended that ephedrine sulfate be formulated only in an aqueous solution, as this formulation was the only one containing ephedrine sulfate of which the Panel was aware (45 FR 35622). However, because the agency is not proposing the Panel's recommendation for final formulation testing, specific vehicles for anorectal active ingredients, including ephedrine sulfate, are not identified in this tentative final monograph. Thus, anorectal active ingredients may be formulated in any safe and suitable vehicle. (See comment 55 below.)

D. Comments on Protectants

17. One comment requested that hydrogenated vegetable oils and waxes be included as Category I anorectal protectants. Another comment requested that semisynthetic bases, such as those derived from coconut oil or mixtures of triglycerides of fatty acids, be recognized as Category I anorectal protectants.

The Panel did not review these substances because no data on them were submitted. The comments did not submit any data to support their requests, nor is the agency aware of any data on these substances when used as anorectal protectant active ingredients. The agency therefore lacks sufficient data for Category I status for these substances at this time.

18. One comment stated that the Panel did not discuss palm kernel oil as a protectant and suppository base, nor did it evaluate two submissions that it received on this ingredient (Refs. 1 and 2). The comment added that the Panel failed to use its expertise to evaluate and designate palm kernel oil as a "protectant vehicle" when the only use of this ingredient that it mentioned was as an inactive ingredient (45 FR 35580). The comment stated that palm kernel oil is combined with other nonirritating oils, such as coconut oil, for use as an ointment base or a suppository base and has been used as a "protectant vehicle" in a therapeutic formulation for the treatment of psoriasis and eczema. The comment referred to published studies on the safety of hydrogenated palm kernel oil as a suppository base and on the rate of release of pharmacologically active ingredients from palm kernel oil ointment bases. The comment stated that the wide use of this protectant ingredient, in addition to the data, attests to its safety for human use topically and internally. The comment provided a bibliographical listing of 17 references to support its statements and copies of 9 of these references (Ref. 3).

The agency has reviewed the submissions cited by the comment and the nine references provided and concludes that the data are inadequate to support the classification of palm kernel oil as a Category I protectant for anorectal use. However, it should be noted that this nonmonograph classification and the Panel's classification of palm kernel oil is an inactive ingredient do not prevent its use in an ointment or suppository base.

One of the submissions referred to by the comment was a letter to the Panel describing a marketed suppository containing a combination of two suppository bases in approximately equal amounts (Ref. 1). The letter also stated that the bases were synthetic triglycerides derived from coconut or palm kernel oil and requested that the Panel include coconut oil and palm kernel oil in its list of pharmaceutical necessities (inactive ingredients). Accordingly, the Panel added these ingredients to its list of pharmaceutical necessities as "coconut oil (palm kernel oil)" (45 FR 35580). The letter did not mention the use of coconut oil or palm kernel oil as protectants.

Subsequently, on May 14, 1975, another submission was made to the Panel by the same manufacturer on its ointment and suppository products (Ref. 2). The submission lists the ingredients of an anorectal ointment and suppository, including the suppository bases described in the letter above. The submission did not make a specific request that these ingredients be considered as protectants nor was any information provided in the submission on the safety and effectiveness of coconut oil or palm kernel oil as protectants.

As mentioned above, the comment provided copies of 9 of the 17 references that it cited. The other 8 references appear to have been published in foreign languages, and the agency has been able to obtain a complete translation for only one of these references (Ref. 4). The data contained in the available references provide general information as to the fatty acid content of the oil, manufacturing processes, chemical and physical properties, and use of the oil in soaps (Refs. 5 through 12).Golucki (Ref. 4) studied the liberation rate of citric acid and salicylic acid from palm kernel oil ointments. These references relate to safety, but do not support the effectiveness of palm kernel oil as a protectant. Interested persons may submit additional data to establish the effectiveness of palm kernel oil as a protectant during the comment period following the publication of this tentative final monograph. Any data received will be evaluated and addressed in the final rule.

The agency's detailed comments and evaluation of the submissions and the references cited by the comment are on file in the Dockets Management Branch (Ref. 13).

References

(1) Letter submitted by Bristol-Myers Products, dated June 17, 1974, to T. DeCillis, FDA, in OTC Volume 12APA3, Docket No. 80N–0050, Dockets Management Branch.

(2) OTC Volume 120031.

(3) Comment No. C00014 and Report No. RPT, Docket No. 80N–0050, Dockets Management Branch.

(4) Golucki, Z. "The Relationship Between the Concentration of a Pharmacologically Active Substance and the Rate of Its Liberation From Ointment Base," *Dissertationes Pharmaceuticae et Pharmacologicae*, 23:83–87, 1971.

(5) Myddleton, W.W., "Cosmetic Materials. Their Origin, Characteristics, Uses and Dermatological Action," Vol. II, "The Principles and Practice of Modern Cosmetics," Chemical Publishing Co., Inc., New York, p. 315, 1963.

(6) Balsam, M.S., and E. Sagarin, "Cosmetics. Science and Technology," 2d Ed., Wiley-Interscience, New York, p. 8, 1972.

(7) Dreger, E. E., and J. Ross, United States Patent No. 2,462,831 (abstract), assigned to Colgate-Palmolive-Peet Co., March 1, 1949.

(8) Wade, A., editor, "Martindale. The Extra Pharmacopoeia," 27th Ed., The Pharmaceutical Press, London, pp. 1049–1050, 1977.

(9) "British Pharmacopoeia—1973," 10th Ed., Medicines Commission, London, pp. 339–340, 1973.

(10) Allen, A., G.H. Padley, and G.R. Whalley, "The Fatty Acid Composition of Some Soapmaking Fats and Oils, Part 2. Coconut and Palm Kernel Oils," *Soap, Perfume, Cosmetics*, 42:372, 374, 376, 378, and 380, 1969.

(11) Cornelius, J.A., "Palm Oil and Palm Kernel Oil," *Progress in the Chemistry of Fats and Other Lipids*, 15:5–27, 1977.

(12) Szczepanska, H., H. Grynberg, and Z. Elsner, "Some Interdependence of Physicochemical and Pharmaceutical Properties of Fats," *Fette-Seifen-Anstrichmittel*, 22:68–71, 1970.

(13) Letter from W.E. Gilbertson, FDA, to W.B. Elvers, Bristol Myers Products, coded LET007, Docket No. 80N–0050, Dockets Management Branch.

19. One comment requested that the advance notice of proposed rulemaking be amended to include cocoa butter substitutes derived from natural food grade coconut and/or palm kernel oils as Category I protectants. Stating that cocoa butter substitutes are currently marketed in OTC anorectal drug products and are more readily available and less costly than cocoa butter, the comment submitted excerpts from pharmaceutical compendia in support of this statement (Refs. 1, 2, and 3). The comment added that cocoa butter substitutes, sometimes referred to in labeling as bland hydrogenated vegetable oil base ("Adeps Solidus"), are contained in suppository products submitted to the Hemorrhoidal Panel, but did not specify any submitted products as containing these ingredients. The comment subsequently submitted copies of an unpublished clinical study (Ref. 4), a published clinical study (Ref. 5), and results of a Draize eye test (Ref. 6).

The agency considered the comment's request as a petition to reopen the administrative record and included the new data and information on cocoa butter substitutes. Subsequently, the agency evaluated these data and information and determined that they relate only to safety and do not address effectiveness. In addition, the composition of cocoa butter substitutes was not defined, nor was a use concentration established. Lacking

specific data to show composition and use concentration of cocoa butter substitutes, the agency cannot evaluate the safety and effectiveness of these ingredients and thus cannot consider them as Category I anorectal protectants.

The compendial references provide general information that describes cocoa butter substitutes as suppository bases (Refs. 1 and 2) or describes physical characteristics of these ingredients, such as melting points, compatibility, etc. (Ref. 3). While these data relate to the safety of cocoa butter substitutes, they do not address the effectiveness of these ingredients as anorectal protectants or adequately define their composition or the optimum concentration for anorectal protectant use. The unpublished clinical study states that 100 cases were studied, but does not mention the ingredient content of the suppositories that were used (Ref. 4). The published study discusses the use of "Adeps solidus" and "oleum cacao" as "suppository compositions" in young dogs and reports no inflammatory reactions (Ref. 5). The results of the Draize eye test showed that a formulation described as "WITEPSOL S58017" can be safely used as a medium for vaginal application of medications, but did not disclose the ingredient content of this formulation. The data are inadequate to establish general recognition of the safety and effectiveness of these ingredients as anorectal protectants.

The agency's detailed comments and evaluations of the above data are on file in the Dockets Management Branch (Ref. 7). In response to the agency's comments, the firm submitted two additional studies on WITEPSOL (Refs. 8 and 9) and a protocol to evaluate cocoa butter substitutes as anorectal protectants (Ref. 10). One study (Ref. 8) compared WITEPSOL to several substances to determine skin irritancy while the other study (Ref. 9) discussed the use of WITEPSOL as a suppository vehicle for the delivery of preanesthetic medication in young children. These data are also inadequate to support the effectiveness of WITEPSOL as an anorectal protectant. The agency's detailed comments and evaluations of these data (Ref. 11) and of the protocol (Ref. 12) are also on file in the Dockets Management Branch. In response to the agency's comments, the firm has submitted additional information (Refs. 13 through 16). This information is currently being evaluated and will be addressed in the final rule.

As noted in comment 18 above, the Panel classified palm kernel oil as an inactive ingredient, but this classification does not prevent use of palm kernel oil as an anorectal suppository base because this is not considered an active ingredient use. Similarly, a cocoa butter substitute derived from food grade coconut oil could be used as a suppository base without being classified as a Category I anorectal active ingredient.

References

(1) "United States Pharmacopeia XX—National Formulary XV," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1029, 1980.

(2) Wade, A., editor, "The Extra Pharmacopeia," 27th Ed., Council of the Pharmaceutical Society of Great Britain, London, p. 1047, 1977.

(3) "European Pharmacopoeia," Vol. III, The Council of Europe, Sainte-Ruffine, France, pp. 139–140, 1975.

(4) Neumann, H., "Clinical Test of the Suppository Composition Imhausen H.," English translation of an unpublished study, included in CP (Citizen Petition), Docket No. 80N–0050, Dockets Management Branch.

(5) Neuwald, F., and J. Meyer-Lohman, "Comparative Test of Compatibility of Adeps Solidus and Oleum Cacao," (English translation), *Arzneimittelforschung*, 8:620–622, 1958.

(6) "A Report Prepared for Dynamit Nobel, A. G., Draize Eye Test," Consultox Laboratories LTD, London, 1970.

(7) Letter from W. E. Gilbertson, FDA, to B. Pagliocca, Kay-Fries, Inc., coded LET008, Docket No. 80N–0050, Dockets Management Branch.

(8) Motoyoshi, K., et al., "Comparative Studies on the Irritancy of Oils and Synthetic Perfumes to the Skin of Rabbit, Guinea Pig, Rat, Miniature Swine and Man," *Cosmetics & Toiletries*, 94:41–48, 1979.

(9) Shochat, S. J., J. Lewin-Epstein, and E. Superstine, "Preanesthetic Suppository for Ambulatory Children: Importance of the Base," *Anesthesia and Analgesia; Current Researches*, 48:427–436, 1969.

(10) Reply Comment coded RC002, Docket No. 80N–0050, Dockets Management Branch.

(11) Letter from W. E. Gilbertson, FDA, to V. Piermattie, Kay-Fries, Inc., coded LET012, Docket No. 80N–0050, Dockets Management Branch.

(12) Letter from W. E. Gilbertson, FDA, to B. Pagliocca, Kay-Fries, Inc., coded LET013, Docket No. 80N–0050, Dockets Management Branch.

(13) Letters from B. Pagliocca, Kay-Fries, Inc., to FDA, coded LET014, LET015, and LET016, Docket No. 80N–0050, Dockets Management Branch.

(14) Letter from J. (Whelan) Nikitakis, CTFA, to Dr. Hulsmann, Dynamit Nobel Aktiengesellschaft, coded LET017, Docket No. 80N–0050, Dockets Management Branch.

(15) Letter from B. Pagliocca, Kay-Fries, Inc., to Dr. Hulsmann, Dynamit Nobel Aktiengesellschaft, coded LET018, Docket No. 80N–0050, Dockets Management Branch.

(16) Letter from Dr. Hulsmann and Mr. Heers, Dynamit Nobel Aktiengesellschaft, to J. Whelan, CTFA, coded LET019, Docket No. 80N–0050, Dockets Management Branch.

20. One comment recommended that the concentration of shark liver oil be lowered to 2 to 10 percent in combination with other protectants instead of the Panel's recommended concentration of at least 50 percent per 2-g dosage unit. The comment argued that the lower concentration would allow the combination of shark liver oil with other protectants so that the total amount of protectants in the product would be at least 50 percent (the Panel's required concentration for making protectant claims), and the amount of vitamin A provided by daily use of the product would not exceed the Panel's recommended daily limit for anorectal use of 10,000 International Units (IU) of vitamin A. The comment referred to a presentation to the Panel showing that a particular marketed product, if labeled according to the Panel's recommended dosage schedule of up to six applications per 24 hours, would provide 150,000 to 210,000 IU of vitamin A, or 15 to 21 times the Panel's recommended maximum daily allowance of 10,000 IU (Ref. 1). The comment stated that, based on the transcript of the Panel's last meeting, the Panel intended that the percentage of shark liver oil should be reduced appropriately so that it could be formulated in combination with other protectants, providing a total protectant combination of at least 50 percent without exceeding 10,000 IU of vitamin A in daily use (Ref. 2).

The Panel noted that in the past, shark liver oil was required to contain not less than 16,500 IU of vitamin A and 40 IU of vitamin D per g of oil, but there is no current standard, and the concentration of vitamin A and vitamin D in shark liver oil may vary (45 FR 35634). According to the transcript of the Panel's last meeting, each g of the shark liver oil used in the product described above contains 25,000 to 35,000 IU of vitamin A (Ref. 2). The Panel also noted at this meeting that 16,500 IU of vitamin A is about the lowest concentration that might be expected to occur in each g of shark liver oil. In either case, one application of a product containing the Panel's recommended shark liver oil concentration of at least 50 percent per 2-g dosage unit would exceed the Panel's maximum daily allowance of 10,000 IU of Vitamin A. Therefore, the agency concurs that shark liver oil should be used in a concentration of less than 50 percent in anorectal drug products.

The Panel concluded that a reasonable maximum allowable concentration for safe OTC topical use is 10,000 IU of Vitamin A and 400 IU of Vitamin D per 24 hours (45 FR 35634).

Because of this safety limitation, the agency is not proposing a dosage as with other protectants, i.e., a contribution of at least 12.5 percent by weight. Instead, the agency is proposing in this tentative final monograph that when shark liver oil is used in anorectal drug products, each product is to be formulated and labeled for use up to six times daily so that the total amount of the product to be applied over a 24-hour period contains 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of vitamin D (now named cholecalciferol). (One U.S.P. unit is equivalent to 1 international unit.) Thus, a single application could contain one-sixth of the 10,000-U.S.P. units maximum daily allowance of vitamin A (1,666⅔ U.S.P. units) and one-sixth of the 400-U.S.P. units maximum daily allowance of cholecalciferol (66⅔ U.S.P. units).

Based on the above safety discussion, the agency is proposing in this tentative final monograph that shark liver oil for protectant use be formulated only in combination with other protectants. This use is consistent with the marketing history of shark liver oil in OTC anorectal drug products and allows a reasonable latitude in the formulation of such products to permit a total protectant content of at least 50 percent without exposing the user to excessive amounts of vitamin A.

Likewise, the agency is proposing the same conditions for cod liver oil for protectant use. Therefore, the Panel's recommended dosage for cod liver oil has been revised to be consistent with the dosage being proposed for shark liver oil, as discussed above.

As discussed in comment 30 below, calamine and zinc oxide, which are limited to concentrations of less than 50 percent, may be used only in combination with other protectants (not to exceed four) in order to assure that the protectant content of the final formulation is at least 50 percent.

References

(1) Transcript of the 29th Meeting of the Advisory Review Panel on OTC Hemorrhoidal Drug Products, January 22–24, 1978, p. 53.

(2) Ibid., pp. 143–148.

E. Comment on Counterirritants

21. One comment, submitted in response to the reopening of the anorectal administrative record to include the Miscellaneous External Panel's statement on camphor-containing drug products (45 FR 63876), objected to that Panel's recommendation that camphor be limited to 360 mg per package, preferably in a child-proof container. The comment maintained that this would be a burdensome restriction for all OTC drug products containing low concentrations of camphor and is not justified in view of these products' long history of safe household use. Another comment stated that the risk exceeds the benefit in many drug uses of camphor and that consumers should no longer be exposed to these uses.

These comments were also submitted to the rulemaking for external analgesic drug products, and the agency adddressed the general issue of the safety of camphor in the tentative final monograph on OTC external analgesic drug products. (See the **Federal Register** of February 8, 1983; 48 FR 5854–5855.) The Hemorrhoidal Panel found camphor not safe and not effective for use in OTC anorectal drug products (45 FR 35642) and placed it in Category II. The agency is retaining the Category II classification in this proposed rule.

F. Comment on Astringents

22. One comment asked whether zinc sulfate can be assumed to be classified in the same category (astringent) as zinc oxide because both are zinc salts and display similar properties.

Zinc sulfate cannot be classified as an astringent at this time because no data have been submitted to show its safety and effectiveness for this use.

G. Comment on Wound-Healing Agents

23. Several comments agreed with the Panel's minority report that supports the OTC use of live yeast cell derivative as a wound-healing agent. The comments stated that adequate data had been provided to the Panel to support the safety and effectiveness of live yeast cell derivative as a wound-healing agent. One comment added that a number of world-renowned wound-healing experts from the United States and Europe met with the Panel in January 1977 and concluded that evidence from the available studies of live yeast cell derivative as a wound-healing agent can be used to support the use of live yeast cell derivative in the anorectal area, and that live yeast cell derivative is an appropriate ingredient in an OTC anorectal drug product. Another comment argued that the claims placed in Category III by the Panel (45 FR 35657) for wound-healing agents are valid Category I claims which should be included in the tentative final monograph. Referring to the Panel's Category III labeling for wound-healing agents, one comment stated that personal experiences in testing a product containing a Category III wound-healing agent had demonstrated that the product accelerated repair and that "with injury comes swelling, with repair, inevitably comes 'shrinkage'."

The agency concurs with the majority of the Panel that the submitted studies on rabbits and white rats, excised human tissue, human fibroblasts, experimental abrasions to human skin, and paired skin grafts of burn wounds suggest a positive influence of live yeast cell derivative on wound healing and that live yeast cell derivative has the characteristics of a wound-healing agent, i.e., increased oxygen uptake, hydroxyproline formation which is associated with collagen biosynthesis, tissue growth, and epithelization. Regarding safety, the Panel noted that no studies of the safety of live yeast cell derivative have been specifically carried out, although no toxicity has been noted when the compound was used in experimental animals and no reports of clinical toxicity have been made or noted in the various clinical studies of the commercial product containing live yeast cell derivative (45 FR 35651). The Panel therefore assumed that the compound is safe for limited use (1 week or less).

Although the agency agrees with the Panel that live yeast cell derivative is safe for use as a wound-healing agent for limited use (1 week or less), there remains a lack of sufficient data on its effectiveness. Data to support the effects of live yeast cell derivative on wound healing of the type proposed for OTC use in human subjects are currently not included in this rulemaking. Since the time the comment period closed following publication of the advance notice of proposed rulemaking, new information, including clinical studies, has been submitted to the rulemaking for OTC skin protectant drug products and will be addressed in that rulemaking. These new data are now under review. With publication of this proposed rule for OTC anorectal drug products, the new information will also be included as part of the administrative record in this rulemaking and will be addressed in the final rule. Therefore, at this time, live yeast cell derivative remains in Category III for effectiveness for use as an OTC wound-healing agent in the anorectal area.

The agency's detailed comments and evaluation of the data currently in the administrative record are on file in the Dockets Management Branch (Ref. 1).

Because the data are insufficient to reclassify wound healing ingredients in Category I, the agency finds that there is insufficient basis at this time to reclassify the labeling claims for these ingredients in Category I, as the comment argued. Should any Category

III wound-healing ingredients be upgraded to Category I, the agency will upgrade the Category III claims recommended by the Panel or develop appropriate label claims based on the data available at that time.

Peference

(1) Letter from W.E. Gilbertson, FDA, to S.F. Barshay, Whitehall Laboratories, coded LET 010, Docket No. 80N-0050, Dockets Management Branch.

H. Comment on Antiseptics.

24. One comment disagreed with the Panel's conclusion that antiseptics should not be included in OTC anorectal drug products because no data had been submitted showing that antiseptics in these products are more effective than soap and water. The comment asserted also that data had not been submitted showing that antiseptics may be harmful when used in these products and pointed out that resorcinol and 8-hydroxyquinoline have both been used safely for many years as antiseptics in its OTC anorectal drug products. The comment maintained that anorectal drug products are often used when soap and water for cleansing the anorectal area are not available and that including antiseptics in these products may help prevent infection or itching.

The Panel concluded that the inclusion of antiseptics in OTC anorectal drug products "is useful in concept," but "that proof of any significant clinical benefit of claimed antiseptic ingredients must be demonstrated in clinical trials" (45 FR 35659). The Panel believed that, because of the large numbers of microorganisms present in feces, there is little likelihood that effective antisepsis could be obtained in the anorectal area with antiseptics any more than with soap and water. The Panel was also concerned about possible toxicity from the absorption of ingredients such as resorcinol through mucous membranes (45 FR 35661) and therefore classified resorcinol in Category III for external use and Category II for intrarectal use. As discussed in comment 7 above, the ingredient 8-hydroxyquinoline was not submitted to the Panel for review. The comment did not submit any data to support the use of these ingredients in particular, or the use of antiseptics in general, in anorectal drug products. Therefore, the agency has no basis for including these ingredients in the tentative final monograph.

I. Comment on Hydrocortisone

25. One comment pointed out that the Panel did not consider the status of hydrocortisone for use in OTC anorectal drug products and requested that this use be clarified because another Panel's recommended labeling for OTC external analgesic drug products containing hydrocortisone included a claim "for itchy genital and anal areas." (See 44 FR 69865.)

Although the Hemorrhoidal Panel did not review and classify hydrocortisone for use as an anorectal active ingredient, in the tentative final monograph for OTC external analgesic drug products (48 FR 5852) the agency proposed the use of hydrocortisone and hydrocortisone acetate in concentrations of 0.25 to 0.5 percent for various types of itching including "anal itching." The agency's proposed indication is similar to the various phrases regarding relief of itching that the Hemorrhoidal Panel recommended as portions of the indications for OTC anorectal drug products. Because a claim for hydrocortisone and hydrocortisone acetate for the temporary relief of anal itching is already included in the OTC external analgesic tentative final monograph, the agency sees no reason to repeat that claim in this tentative final monograph. Further, the agency believes that, whenever possible, various related conditions for which an ingredient is considered generally recognized as safe and effective for OTC use should be listed in a single appropriate monograph, which, in this case, is the monograph for OTC external analgesic drug products.

The agency does, however, note that the Hemorrhoidal Panel recommended specific warnings and directions for products labeled to relieve itching in the anal area. These include specific warnings to consult a physician promptly in case of bleeding and to cleanse the anorectal area, when practical, before applying the product. The agency is adopting these warnings and directions in this tentative final monograph. The agency believes that any hydrocortisone-containing (or any other) drug product labeled for the relief of anal itching should bear appropriate warnings and directions information. Therefore, in a future issue of the **Federal Register**, the agency will amend the tentative final monograph for OTC external analgesic drug products so that products containing ingredients subject to that monograph that bear claims for the relief of "anal itching" also bear the appropriate warnings and directions contained in § 346.50 (c)(2), (3), and (4) and (d)(1) of this tentative final monograph for anorectal drug products.

J. Comment on Inactive Ingredients

26. One comment stated that bismuth subgallate, classified by the Panel as a protectant when present in a product in at least 50 percent of a 2-g dosage unit, should also be classified as an inactive ingredient (or pharmaceutical necessity) when included in an anorectal drug product in small quantities. The comment stated that a marketed suppository contains a small quantity of bismuth subgallate as a stiffening agent and that no protectant labeling claim is made for this product.

Bismuth subgallate was classified by the Panel as a Category III protectant active ingredient for external and intrarectal use in a concentration of 17.5 to 166 mg per dosage unit, not to exceed 1 g per 24 hours (45 FR 35639). The Category III classification of bismuth subgallate would not preclude its use as a pharmaceutical necessity so long as the labeling of the product does not refer to bismuth subgallate as an active ingredient or associate it with any protectant activity. The agency concurs with the comment that bismuth subgallate could be an inactive ingredient when used as a stiffening agent in a suppository dosage form.

K. Comments on Dosage

27. One comment expressed concern that the Panel implied that a 2-g dosage unit is the size of choice for delivery to the anorectal area. The comment emphasized that, although studies may have shown that an average of 2 g of a product is used, a 2-g dosage unit should not be mandated as the standard.

The Panel stated at 45 FR 35591 that "a 2-gram dosage unit is reasonable, but this does not imply that other dosage sizes are not acceptable". The Panel also cited an official compendium as stating that the average adult suppository weighs 2 g (Ref. 1) and added that in studies reviewed by the Panel, patients used an average of 2 g of ointment per application (Ref. 2). The Panel recognized that exceptions to dosage unit size do occur, and its recommended monograph did not specify that dosage units be limited to 2 g. The agency agrees with the Panel and is not proposing a standard dosage unit in this tentative final monogaph.

References

(1) "The United States Pharmacopeia," 19th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 704, 1975.

(2) OTC Volume 120022.

28. One comment contended that there is no basis in the Panel's report, or in any of the references cited, for limiting the dosage of petrolatum in

§ 346.56(d)(11), which reads: "* * * not to exceed six applications per 24 hours or after each bowel movement." Arguing that the proposed dosage limitation is misleading because petrolatum poses a very low risk to health from overuse, the comment requested that the dosage for petrolatum be "use as needed."

The agency agrees with the comment that there is no basis in the Panel's report, or on record, for limiting the dosage of petrolatum and that the ingredient is safe when applied liberally as needed. Petrolatum is relatively inert and is not absorbed through intact or broken skin or mucous membranes. Its safety has been established by decades of use as a base for anorectal and other medications and as a skin protectant. The agency believes that the directions for use for petrolatum in this tentative final monograph should be the same as those in the skin protectant tentative final monograph (published in the **Federal Register** of February 15, 1983; 48 FR 6820) and therefore is proposing that § 346.56(d)(6) of this tentative final monograph read: "Apply liberally as often as necessary."

29. One comment disagreed with the Panel's recommended dosage in § 346.14(k) of "50 percent or greater per dosage unit" to justify a protectant claim for petrolatum. The comment stated that the Panel incorrectly interpreted the studies cited on transepidermal water loss (45 FR 35627) and that protection can be obtained at a much lower film thickness than calculated by the Panel. The comment cited an oral presentation made to the Panel in which it was explained that only by specifying a dose could a concentration figure have meaning (Ref. 1). The comment provided an example to show that protection can be obtained from as little as a 25-percent concentration in a dosage unit.

The agency has reviewed the Panel's discussion of protectants (45 FR 35627), the Panel's discussion of petrolatum (45 FR 35634), and the presentation made by Dr. M. Berdick (Ref. 1). The agency concludes that the Panel's recommendation for a 50-percent or greater concentration of protectants per 2 g dosage unit provides a reasonable basis for establishing the minimum quantity of a protectant that is necessary to provide relief. The Panel also discussed the possibility that testing might establish that a protectant could achieve the same effect at a lower concentration (45 FR 35628). However, the comment did not submit any clinical data to support a 25-percent concentration. Therefore, the agency proposes to adopt the Panel's recommendation of a 50-percent or greater concentration for most anorectal protectants, including petrolatum. (See comments 20 above and 30 below.)

Reference

(1) Summary Minutes of the 27th Meeting of the Advisory Review Panel on OTC Hemorrhoidal Drug Products, April 29 and 30, 1977, OTC Volume 12APA2.

30. Several comments noted that there appeared to be an inconsistency in the Panel's recommended monograph between the concentration of protectants when used as single ingredients and when used in combination. The comment believed that the Panel intended "that to justify a claim for protectant effect a combination of two but not more than four protectants must be present for a combined concentration of at least 50 percent." The comments requested that recommended §§ 346.14 and 346.22 be clarified and made consistent with the Panel's intent that the combined concentration of protectants be at least 50 percent.

The Panel concluded that to justify a claim for protectant effect, either of the following criteria must be met: (1) At least one protectant must be present to provide at least 50 percent by weight (1 g of a 2-g dosage unit); or (2) a combination of two but not more than four protectants must be present to provide at least 50 percent by weight (1 g of a 2-g dosage unit). (See 45 FR 35627.) The Panel believed that a minimum of 50 percent by weight (1 g of a 2-g dosage unit) would still permit the addition of other active ingredients as well as any inactive ingredients that may be necessary to formulate a pharmaceutically acceptable preparation (45 FR 35628).

The Panel determined that for certain protectant ingredients limited to concentrations of less than 50 percent the data submitted to the Panel indicated that these ingredients are usually present in combination with other protectant ingredients (45 FR 35592). Therefore, the agency concludes that the intent of the Panel was that these ingredients, because of their physical characteristics, cannot be used as single ingredients but may be used only in combination with other protectants in order to meet the Panel's recommended minimum protectant content per dosage unit, i.e., 50 percent concentration by weight (1 g of a 2-g dosage unit). Accordingly, the agency is clarifying the Panel's recommendation and is proposing in § 346.14(b) of this tentative final monograph that calamine, cod liver oil, shark liver oil, and zinc oxide be used only in combination with other protectants.

The Panel believed that limiting combinations of protectants to two but not more than four protectants would provide reasonable latitude in the formulation of anorectal products because only four products submitted to the Panel had four or more protectant ingredients. However, because the Panel did not establish a concentration range for all protectant ingredients, the agency believes it is reasonable to propose that certain protectant ingredients (aluminum hydroxide gel, cocoa butter, glycerin (20 to 45 percent aqueous solution), kaolin, lanolin, mineral oil, petrolatum, starch, and white petrolatum) be limited to a minimum concentration that contributes at least 12.5 percent by weight of the final dosage unit (0.25 g of a 2-g dosage unit). This will enable the formulation of combinations of up to 4 protectants without permitting inactive levels of ingredients to be included and will meet the Panel's recommended minimum combined protectant concentration of 50 percent per dosage unit.

Consistent with this determination, the agency is proposing that the minimum allowable amount of calamine or zinc oxide in a combination also be 12.5 percent by weight. In addition, because the dosage for calamine is calculated on its zinc oxide content and because both calamine and zinc oxide are classified as Category I anorectal astringents as well as anorectal protectants, the agency concludes that the combined weight of zinc oxide in any anorectal combination product should not exceed the maximum safe concentration of zinc oxide recommended by the Panel, i.e., 25 percent by weight per dosage unit. Cod liver oil and shark liver oil should be present in a combination drug product in accord with the dosage discussed in comment 20 above.

Accordingly, recommended § 346.22 (redesignated as § 346.22(a) in this tentative final monograph) is revised to read as follows: "Any two, three, or four protectants identified in § 346.14 may be combined, provided that the combined percentage by weight of all protectants in the combination is at least 50 percent of the final product (1 gram of a 2-gram dosage unit). Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5 percent by weight (0.25 gram of a 2-gram dosage unit). If an ingredient in § 346.14(b) is included in the combination, it must not exceed the concentration limit specified in § 346.14(b)." In addition, new § 346.22(c) has been added to this tentative final monograph as follows: "Any product

containing calamine for use as a protectant and/or as an astringent and/or containing zinc oxide for use as a protectant and/or as an astringent may not have a total weight of zinc oxide exceeding 25 percent by weight per dosage unit."

L. Comments on Combinations.

31. Several comments objected to the Panel's recommended requirement that a combination of Category I anorectal active ingredients be shown safe and effective in final formulation testing. The comments particularly objected to the Panel's recommendation that final formulation testing for effectiveness of a combination "should demonstrate in clinical trials that there is a statistically significant difference in effectiveness of the combination for relief of a symptom as compared to the combination without each of the active ingredients, excluding protectants" (45 FR 35594). The comments argued that such testing of combinations is unprecedented and arbitrary and is neither called for in the agency's combination policy as set forth in § 330.10(a)(4)(iv), nor consistent with the FDA general guidelines for OTC combination drug products (Ref. 1).

The comments asserted that the combination policy for anorectal active ingredients could be made meaningful by deleting final formulation testing and basing decisions regarding safety and effectiveness of combinations on the evaluation of their active ingredients. The comments noted that the Panel placed in Category III a number of combinations of Category I ingredients from different therapeutic categories and that these combinations would have been considered Category I were it not for the requirement of final formulation testing. (See 45 FR 35593, part II. paragraphs K.10.a. (1), (2), and (3).) The comments requested that these combinations be placed in Category I.

As discussed in comment 55 below, the agency is not requiring final formulation testing of either single-ingredient or combination anorectal drug products. As a result, the agency is not requiring clinical trials to demonstrate a statistically significant difference in effectiveness between the combination in final formulation and the combination without each active ingredient.

The regulations at § 330.10(a)(4)(iv) state that an OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population. In addition, paragraph (1) of the agency's general guidelines (Ref. 1), which were not available at the time of the Panel's deliberations, provides for the combination of Category I active ingredients from different therapeutic categories to treat different symptoms concurrently if each ingredient is present within its established safe and effective dosage range and the combination meets the OTC combination policy in § 330.10(a)(4)(iv) in all other respects. Therefore, the agency is proposing that the combinations of Category I ingredients from up to three different therapeutic categories (except protectants) that the Panel placed in Category III pending final formulation testing be reclassified in Category I consistent with § 330.10(a)(4)(iv) and the agency's supplementary guidelines for OTC combination drug products (Ref. 1).

The combination of up to four protectants identified in § 346.22 of the Panel's recommended monograph is redesignated § 346.22(a) in this tentative final monograph. As discussed above, the agency is proposing that the following combinations be included in the designated paragraphs of § 346.24 of this tentative final monograph:

(b) Any single anorectal ingredient identified in § 346.10, § 346.12, § 346.16, § 346.18, or § 346.20 may be combined with up to four protectants in accordance with paragraph (a) of this section.

(c) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12.

(d) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18.

(e) Any single local anesthetic identified in § 346.10 may be combined with any single keratolytic identified in § 346.20.

(f) Any single vasoconstrictor identified in § 346.12 may be combined with any single astringent identified in § 346.18.

(g) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18.

(h) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single keratolytic identified in § 346.20.

(i) Any single astringent identified in § 346.18 may be combined with any single keratolytic identified in § 346.20.

(j) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12 and with any single astringent identified in § 346.18.

(k) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(l) Any single vasoconstrictor identified in § 346.12 may be combined with any single analgesic, anesthetic, and antipruritic identified in § 346.16 and with any single astringent identified in § 346.18.

(m) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(n) Any combination of ingredients listed in paragraphs (c) through (m) of this section may be combined with up to four protectants in accordance with paragraph (a) of this section.

The redesignation of the term "counterirritant" to "analgesic, anesthetic, and antipruritic" is discussed in Part II.B.6 below—*Summary of the Agency's Changes in the Panel's Recommendations.* The Panel's classification of combinations of more than three Category I ingredients from different pharmacologic groups, except protectants, is discussed in comment 32 below.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

32. Two comments objected to the Panel's recommendation to limit the number of ingredients included in hemorrhoidal preparations. The comments stated that limiting ingredients to only three pharmacological groups is unscientific, uncorroborated, and arbitrary. One comment maintained that limiting hemorrhoidal preparations to four or fewer nonprotectant active ingredients would tend to make them "fungible" and would discourage ingenuity in the development of combination products. The comment argued that these recommendations contradict FDA guidelines for combination drug products in § 330.10(a)(4)(iv). The comments recommended that a fixed limit not be arbitrarily placed upon the

number of active ingredients in a combination of hemorrhoidal ingredients when there is evidence that the combination is rational, safe, and effective with a suitable target population. One comment stated, as an example, that a product containing a vasoconstrictor to shrink hemorrhoids, a local anesthetic to deaden pain, a protectant to soothe the irritated area, a counterirritant to cool the irritated area until the local anesthetic can take effect, and an antiseptic to help prevent infection and help relieve itching would be beneficial to many hemorrhoid sufferers.

The agency agrees with the comments that a fixed limit need not be placed upon the number of active ingredients in a combination product if it can be shown to be a rational, safe, and effective combination with a suitable target population. This position is consistent with FDA policy for OTC combination drug products in § 330.10(a)(4)(iv) and with the guidelines for combinations (Ref. 1). However, the agency believes that the interest of consumers is best served if the desired therapeutic effect is achieved safely and effectively by the smallest number of active ingredients.

The Panel placed certain two-ingredient and three-ingredient combination products in Category III pending final formulation testing (45 FR 35593). Because the agency is not adopting the Panel's requirements for final formulation testing, the agency is proposing that these combinations be Category I in this tentative final monograph. (See comment 31 above.) The agency will consider any other combinations for Category I, regardless of the number of ingredients and the formulation, provided adequate data are presented in accordance with the combination policy and the guidelines mentioned above. The specific combination of five ingredients cited by one comment has not been included in this tentative final monograph because the comment submitted no data for the agency to evaluate.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D-0322, Dockets Management Branch.

33. One comment suggested revising the Panel's language in Part II. paragraph K.8.d.—Criteria for Category I combination products for external and/or intrarectal use, which reads as follows: "Products that do not claim protectant activity and contain one Category I active ingredient from each pharmacologic group in the combinations identified below are classified as Category I combination products, provided that (1) the active ingredients and their labeling are generally recognized as safe and effective, (2) such ingredients are present in amounts within the effective dosage range, and (3) the final formulation has been shown to be safe and effective."

The comment suggested revising the first part of this paragraph to read "Combinations of Category I active ingredients each from a different pharmacologic group identified below, combined with or without one or more protectants, are classified as Category I combination products * * * *" In addition, the comment recommended that paragraph K.10.a.(1), which reads "Combinations containing any single Category I active ingredient and one or more protectants," be moved to paragraph K.8.d., and a new paragraph K.8.e. be added to read as follows: "Any single Category I active ingredient and one or more protectants."

The combinations referred to in paragraphs K.8.d. and K.10.a. of the Panel's report are the same combinations of Category I ingredients from different therapeutic categories that the agency is proposing as Category I in § 346.22 (b) through (n) of this tentative final monograph. Therefore, the comment's suggested revisions of the Panel's report are not necessary. (See comment 31 above.)

34. One comment objected to the Panel's conclusion that the combination of a local anesthetic and a counterirritant in a hemorrhoidal drug product is irrational (45 FR 35593). The comment argued that, although the Panel acknowledged that the onset of action of the local anesthetic may be briefly preceded by the action of the counterirritant, it ignored the importance of "fast, cooling relief, even if superseded by another ingredient's soothing effect later." The comment stated that a counterirritant and a local anesthetic should be combined in a hemorrhoidal product if the inclusion of both ingredients results in any extra relief and satisfaction for the user. The comment stated that it was not aware of any adverse reactions to menthol when used as a counterirritant in the strength used in its rectal ointments.

The Panel concluded that the simultaneous use of a counterirritant (such as menthol) and a local anesthetic is irrational. The mechanism of action of a counterirritant is dependent upon an intact nerve function, but nerve function is specifically blocked by an effective local anesthetic. The action of a counterirritant that may briefly precede the action of a local anesthetic is not sufficient justification for the combination.

The agency concurs with the Panel and notes that the Topical Analgesic Panel in its report on external analgesic drug products also classified the combination of a local anesthetic and a counterirritant in Category II. The Topical Analgesic Panel concluded that it is irrational to combine pharmacologic groups that act in opposition to each other and that such a combination may be unsafe (44 FR 69790). No comments objecting to that Panel's conclusions were submitted during the comment period following the publication of the Panel's report. In the tentative final monograph on OTC external analgesic drug products (48 FR 5852), the agency reaffirmed that Panel's Category II classification for this combination.

The Hemorrhoidal Panel concluded that menthol is safe and effective for external use as a counterirritant (45 FR 35641). The Panel also concluded that menthol is safe but not effective for intrarectal use (45 FR 35643); the agency concurs.

The deciding factor for the Category II classification of the combination of a local anesthetic and a counterirritant was not the safety of menthol as a counterirritant, but rather the lack of medical rationale for combining these two pharmacologic groups.

35. One comment recommended that the tentative final monograph for anorectal drug products include the combination of live yeast cell derivative and protectants, including shark liver oil.

The Panel classified live yeast cell derivative in Category III as a wound-healing agent in anorectal drug products and recommended that if a Category III ingredient is present in a combination product containing no Category II ingredient, the combination is classified as Category III (45 FR 35593 and 35594). On the basis of the Panel's combination policy, the combination of live yeast cell derivative and any Category I protectant, such as shark liver oil, is a Category III combination. The Panel's recommendation is consistent with the agency's policy for combination drug products in § 330.10(a)(4)(iv) and the combination guidelines (Ref. 1). Live yeast cell derivative remains in Category III in this tentative final monograph; therefore the agency considers the combination of live yeast cell derivative and any Category I protectant to be a Category III combination product at this time. (See comment 23 above.)

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D-0322, Dockets Management Branch.

M. Comments on Labeling of Anorectal Drug Products

36. Two comments stated that existing statutory provisions (15 U.S.C. 1453(a), 21 CFR 201.61, and sections 508 and 502(e) of the Federal Food, Drug, and Cosmetic Act) do not show a congressional intent to authorize FDA to legislate the exact wording of OTC drug claims to the exclusion of other equally accurate and truthful claims for these products, and that section 502(c) of the act demonstrates a congressional intent to the contrary. The comments maintained that there are truthful phrases, other than those recommended by the Panel, that would be in keeping with the conclusions of the Panel.

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under 21 CFR 330.1(c)(2), the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the labeling provisions in § 330.1(c)(2).

37. Several comments objected to the Panel's recommendation that all inactive ingredients be listed in the labeling of OTC anorectal drug products. The comments argued that a list of inactive ingredients in the labeling would be meaningless, confusing, and misleading to most consumers. The comments noted that the act does not require that inactive ingredients of drug products be included in labeling and argued that listing these ingredients would obscure information that is more meaningful to consumers.

Two of the comments also cited the warning recommended by the Panel in § 346.50(c)(5) for anorectal drug products containing perfume as an example of labeling related to inactive ingredients that should not be required. This warning states, "If redness, burning, itching, swelling, pain, or other symptoms develop or increase, discontinue use and consult a physician." One comment stated that the warning would be confusing to consumers because the symptoms identified in the warning are the same as those that the product is intended to treat and that such symptoms obviously will already be present. Two of the comments pointed out that neither cosmetic products nor soaps are required to contain a warning statement to indicate their perfume content.

The agency agrees that the Federal Food, Drug, and Cosmetic Act does not require the identification of all inactive ingredients in the labeling of OTC drug products. Section 502(e) (21 U.S.C. 352(e)) does require disclosure of active ingredients and of certain ingredients, whether included as active or inactive components in a product. Although the act does not require the disclosure of all inactive ingredients in the labeling of OTC drug products, the agency agrees with the Panel that listing of inactive ingredients in OTC drug product labeling would be useful information for some consumers. Consumers with known allergies or intolerances to certain ingredients would then be able to identify substances that they may wish to avoid.

The Proprietary Association, the trade association that represents approximately 85 OTC drug manufacturers who reportedly market between 90 and 95 percent of volume of all OTC drug products sold in the United States, has established guidelines (Ref. 1) for its member companies to list voluntarily inactive ingredients in the labeling of OTC drug products. Under another voluntary program begun in 1974, the member companies of The Proprietary Association have been including the quantities of active ingredients on OTC drug labels. The agency is not at this time proposing to require the listing of inactive ingredients in OTC drug product labeling. However, the agency commends these voluntary efforts and urges all other OTC drug manufacturers to similarly label their products.

If a safety problem has been demonstrated for an inactive ingredient, the agency will take appropriate action. (See 21 CFR 201.20.) Because perfumes are considered to be inactive ingredients and because the Panel did not establish that a safety problem exists for specific perfumes, the agency is not proposing the Panel's recommended warning in this tentative final monograph.

Reference

(1) "Guidelines for Disclosure of Inactive Ingredients in OTC Medicines," The Proprietary Association, Washington, DC, July 12, 1984, copy included in OTC Volume 12ATFM.

38. Four comments objected to the Panel's recommendation that the term "anorectal" be used in the statement of identity (§ 346.50(a)) and urged the agency to use instead the more familiar term "hemorrhoidal." To support this position, two comments submitted the results of a survey of 144 consumers aged 18 and older to determine what percentage of consumers understand the word "anorectal." According to one comment, the survey results indicated that 70 percent of the consumers did not understand the term "anorectal." The comments further argued that using the term "hemorrhoidal" would eliminate confusion and aid consumers in purchasing a product to help treat specific symptomology. One comment stated that the term "hemorrhoid" has come to mean more than clinically defined hemorrhoids and that consumers understand this term as encompassing various kinds of anorectal discomforts and disorders. Another comment disliked the popular use of the terms "piles" and "hemorrhoids" and commended the Panel for educating the public by properly defining terms used to describe anorectal disorders.

The agency could not evaluate the merits of the survey because only the results were submitted, and no details were included. However, the agency agrees with the comments in principle that the term "hemorrhoidal" is more familiar and understandable to consumers than the term "anorectal." The agency further believes it is important to educate the consumer as to the proper use of these products. The Panel recommended that anorectal products be labeled for the relief of symptoms associated with hemorrhoids, piles, and other anorectal disorders and stated that consumers must be able to understand the information presented in labeling in order to use these products safely and effectively. Therefore, the agency is proposing that the term "hemorrhoidal" may appear alone or in

parentheses next to the term "anorectal" in the statement of identity for all OTC anorectal drug products in § 346.50(a). In addition, the dosage form, e.g., cream, lotion, or ointment, may be included in the statement of identity.

39. One comment pointed out that several statements of identity could be required for petrolatum because the review of this multipurpose ingredient by several OTC advisory review panels has resulted in multiple labeling requirements. The comment noted that statements of identity of "skin protectant" and "anorectal agent" or "anorectal product" have already been recommended and that additional statements of identity are yet to come in other monographs. The comment recognized the need for a statement of identity in the labeling of every OTC drug product, but argued that the agency should allow a single statement of identity for a multipurpose ingredient such as petrolatum. The comment contended that a statement such as "topical protectant and lubricant" would adequately cover every OTC drug use of petrolatum and would also satisfy the requirements of § 201.61(b) (21 CFR 201.61(b)).

Petrolatum has been placed in Category I by advisory review panels for the following OTC uses: Ophthalmic emollient, anorectal agent, and skin protectant. Ophthalmic drug products containing petrolatum are sterile to avoid the risk of contamination and usually are marketed with indications for ophthalmic use only, but other OTC drug products containing petrolatum could be labeled for both anorectal and skin protectant use. The comment's recommended statement of identity, "topical protectant and lubricant," does not make clear that such a product could be used anorectally and therefore does not fully satisfy the requirements of § 201.61(b). Concerning the comment's suggestion to use "lubricant" in a statement of identity for petrolatum, the agency stated in the tentative final monograph for OTC skin protectant drug products that the term "lubrication" is a cosmetic claim. (See the **Federal Register** of February 15, 1983; 48 FR 6828.) Likewise, the agency believes that "lubricant" is inappropriate in a statement of identity for OTC anorectal drug products.

To make it clear to consumers that the product could be used both as an anorectal agent and as a skin protectant, its labeling should contain the statement of identity, indications, warnings, and directions for use from both rulemakings. As an alternative, manufacturers may choose to label the product for only one of its intended uses.

In this tentative final monograph, the agency is proposing that the statement of identity for petrolatum be "anorectal (hemorrhoidal)," "hemorrhoidal," "anorectal (hemorrhoidal) (insert dosage form, e. g., cream, lotion, or ointment)," or "hemorrhoidal (insert dosage form, e.g., cream, lotion, or ointment)." (See comment 38 above.) A combined statement of identity recognizing the uses established in both monographs, e.g., "anorectal (hemorrhoidal)/skin protectant," would not be burdensome and would meet the requirements of § 201.61(b).

40. One comment suggested that, to eliminate duplication of words or phrases, § 346.50(b) be revised to permit combining the many indications recommended by the Panel, provided that the combined statement is clear and understandable with no change in meaning or emphasis.

The agency agrees with the comment and, consistent with the format and style used in other recently published tentative final monographs, proposes to revise the general indication for all anorectal drug products in § 346.50(b) as follows: ("For the temporary relief of," "Gives temporary relief of," or "Helps relieve the") [as an option, select neither, one, or both of the following: "local" or "anorectal"] [select one or more of the following: "discomfort," "itching," or "itching and discomfort," followed by: "associated with" (select one or more of the following: "hemorrhoids," "anorectal disorders," "inflamed hemorrhoidal tissues," "hemorrhoidal tissues," "anorectal inflammation," or "piles (hemorrhoids).")] (See part II. paragraph B.9. below.)

In addition the agency has also revised the indications statements recommended by the Panel for specific therapeutic groups for clarity and to eliminate duplicative words and phases as appropriate.

41. One comment questioned why the Panel did not include the claim "shrinks hemorrhoids" for anorectal drug products containing zinc oxide and other astringents. The comment cited the following statement from a medical reference (Ref. 1): "This 'astringent' (drawing together) action is characterized by visible contraction of the tissue, blanching and wrinkling of mucous membranes * * *. The principal astringents are: metallic salts * * *." The comment stated that zinc salts, particularly zinc oxide, are considered typical and effective astringents, and requested that the labeling claim "shrinks hemorrhoids" be allowed for anorectal preparations containing such astringents.

The Panel did not specifically address the claim "shrinks hemorrhoids" in relation to anorectal astringents. However, in its general discussion of astringents, the Panel concluded that an effect of astringents is a "decrease in cell volume (implying a reduction in swelling)," but that this effect is not sufficient to warrant a labeling claim for the reduction of swelling (45 FR 35645 and 35649).

In its discussion of Category II labeling for vasoconstrictors, the Panel stated that the applicability of claims such as "shrinks hemorrhoids" for certain combinations of ingredients rested primarily on a definition of the word "shrink" (45 FR 35626). Although the Panel generally agreed that the word "shrink" refers to a reduction in size, there were differing opinions on whether this signifies a temporary phenomenon or implies a permanent change. The Panel stated that consumers would probably consider that a permanent change is to be expected. However, data submitted to the Panel indicated that vasoconstrictors produce a temporary reduction in swelling, and rebound swelling may occur in the long run. Thus, the Panel found that an anorectal vasoconstrictor can "temporarily reduce swelling" or "temporarily shrinks" and that these words sufficiently conveyed the usefulness of vasoconstrictors in the short-term treatment of anorectal symptoms (45 FR 35626). The agency concurs. (See the indications for vasoconstrictors in § 346.50(b)(2)(ii) of the tentative final monograph.)

The comment did not submit any data to show that astringents effectively shrink hemorrhoids even temporarily. Therefore, the agency has no basis for including the requested claim for anorectal astringents in this tentative final monograph.

Reference

(1) Sollman, T., "Local Irritants, Corrosives and Astringents," in "A Manual of Pharmacology," W.B. Saunders Co., Philadelphia, p. 139, 1957.

42. Three comments objected to the Panel's recommendation in § 346.50(c) that warning statements be placed in a "box border" and printed in black ink or the most prominent color of the label. The comments argued that a "box border" is not only inappropriate but also counterproductive because indiscriminately highlighting multiple minor warnings, such as those recommended by the Panel, would increase the probability that serious

hazards will be ignored in other situations. Two of the comments argued that there are no warnings regarding the use of anorectal preparations that justify a "box border" requirement. The comments stated that FDA specifies only two uses for "box borders": To convey important information to physicians regarding indications for drugs found to be less than effective in the Drug Efficacy Study (21 CFR 201.200), and to warn against serious or even life-threatening toxic effects of prescription drugs (21 CFR 201.316).

The agency agrees with the comments that a "box border" should be reserved for special information that should be highlighted to prevent potential serious hazards. This requirement is not justified for any of the OTC anorectal drug product warnings, and in fact there have been only two instances so far in the OTC drug review in which the agency believed a "box border" was justified. The first instance was in the tentative final monograph for OTC emetic drug products, published in the **Federal Register** of September 5, 1978 (43 FR 39544), in which the agency proposed that the warning "Call a physician, Poison Control Center, or emergency room for advice before using, and call immediately if vomiting does not occur within 20 minutes after a second dose has been given" be printed in red and conspicuously boxed. The second instance was in the **Federal Register** of May 1, 1986 (51 FR 16258) in which the agency published a final rule that amended the exclusivity policy and established new labeling requirements for OTC drug products. The final rule provides manufacturers three alternatives for the labeling of OTC drug products. One of those alternatives provides that the label and labeling contain in a prominent and conspicuous location indications for use that have been established under a final OTC drug monograph. At the option of the manufacturer, this labeling may be designated "APPROVED USES," or be given a similar permitted designation, each time it appears in the labeling. If the "APPROVED USES" or a similar designation is used, the labeling involved shall appear within a boxed area. Other applicable labeling, e.g., warnings and directions, may be included in the boxed area, in which case the boxed area shall be designated "APPROVED INFORMATION" rather than "APPROVED USES."

As the comment noted, the Panel also recommended that warnings on anorectal drug products be printed in a special type, size, or color or be illustrated to aid consumers. The agency does not believe that these recommendations are necessary to ensure proper labeling of these products and is not including them in this tentative final monograph.

43. Two comments requested deletion of the pregnancy warning recommended by the Panel in § 346.50(c)(7)(i) for all intrarectal products except protectants. The warning states, "The safety of this product has not been established for use by pregnant women or by nursing mothers." The comments stated that the Panel had no evidence to show any risk to pregnant or nursing women from the use of intrarectal products. One comment contended that the Panel was "merely expressing its belief that it is a good policy for pregnant or nursing women to take no more drugs than are essential." The comment stated that warnings based on a speculative hypothesis would only serve to dilute the importance of other warnings and that if the Panel's warning were heeded, pregnant women would be deprived of the use of products that could relieve some of the major discomforts of pregnancy.

A final rule requiring a warning concerning the use of OTC drugs by pregnant or nursing women was published in the **Federal Register** of December 3, 1982 (47 FR 54750). This warning (21 CFR 201.63) is specific to OTC drugs that are intended for systemic absorption and therefore is not required for OTC anorectal drug products that are intended for local effect.

44. Three comments objected to the Panel's recommended 7-day use limitation in § 346.50(c)(1), "If symptoms do not improve, do not use this product for more than 7 days and consult a physician." Two of the comments contended that this limitation is arbitrary and unsupported by documentation. The third comment contended that minor anorectal conditions normally are amenable to a 2-week treatment period before a doctor should be consulted.

The purpose of a limitation-of-use statement on a product is to inform the consumer of the period of time that is reasonable to allow for symptoms to begin to show improvement or to clear. The Panel concluded that symptoms of minor anorectal disorders that can be self-treated should be significantly relieved, if not completely cleared, in 7 days. The Panel was concerned that the continued self-treatment of the symptoms associated with hemorrhoids and other anorectal conditions may mask more serious medical problems, such as anal fissures, fistulae, abscesses, anal warts, or fecal impactions. The Panel believed that if symptoms do not respond to self-treatment in 7 days, the condition could be a serious one, requiring professional diagnosis and treatment.

The comments did not submit any data to show that more than 7 days may be required to obtain benefits from OTC anorectal drug products. Therefore, the agency proposes that the 7-day limitation be retained, but is revising this warning to advise consumers that a doctor should also be consulted if the condition worsens. The revised warning is proposed as follows: "If condition worsens or does not improve within 7 days, consult a doctor."

45. Two comments suggested revising the Panel's recommended warning statement in § 346.50(c)(7)(ii) that is specific to intrarectal products to be used with special applicators, such as pile pipes or other mechanical devices. The warning states, "Do not use this product if the introduction into the rectum causes additional pain. Consult a physician promptly." One of the comments contended that less trauma would result by applying the product intrarectally with the fingers and suggested that the warning state, "If use of (device) is painful, apply with fingers." The other comment noted that no comparable warning was proposed for suppositories, which usually cause some initial discomfort upon insertion, and suggested that the warning be deleted or altered to reflect common use conditions for products used with applicators.

The Panel stated that special applicators, such as pile pipes, are used to allow the introduction of a preparation above the anal sphincter so that it may remain in contact with the rectal mucosa where attempted insertion of an ointment by the finger is not apt to be successful (45 FR 35589). However, the Panel was concerned that there is some danger that the rectal mucosa can be perforated if a special applicator, such as a pile pipe, is not inserted into the rectum correctly. Accordingly, the Panel believed that the warning it recommended was necessary to alert consumers that there should not be any additional pain (caused by further injury) with the use of a pile pipe. The warning was not intended, as suggested by the comment, to alert consumers about any discomfort that may occur from the insertion of a pile pipe or a suppository. The agency agrees with the Panel that the warning is beneficial but is revising it for clarity as follows: "Do not use this product with an applicator if the introduction of the

applicator into the rectum causes additional pain. Consult a doctor promptly."

46. One comment stated that the Panel did not adequately define the terms "internal" and "external" for the purpose of describing "locus and necessary sites of treatment of anal/rectal irritation." The comment contended that many of the Panel's statements "imply that the entire anal canal is a portion of the anal/rectal 'interior,' " but that this "interior" area is not a proper location for application of certain hemorrhoidal ingredients. The comment objected to the Panel's recommended warnings in § 346.52(c)(2) for hemorrhoidal products containing local anesthetics for external use only, "*Caution:* This product is for external use only. Do not apply inside the rectum in any way," and in § 346.50(c)(6) for products for external use only, "Do not put this product into the rectum by using fingers or any mechanical device or applicator."

The comment argued that these warnings can be construed by the general public as prohibiting insertion of certain hemorrhoidal drug preparations into the anal canal, but that this apparently was not the Panel's intended meaning. The comment added that if these warnings go uncorrected, misinterpretation by the general public "will result in a great deal of unalleviated consumer 'hemorrhoidal' discomfort." The comment stated that pain stemming from irritation in the anal canal below the mucocutaneous junction can be effectively treated only by "internal" application (insertion through the anal canal and into the rectum) of a hemorrhoidal drug preparation. The comment described certain suppositories and ointments that liquefy when inserted and then work their way down, through, and over the cutaneous area below the mucocutaneous junction. The comment contended that the Panel's conclusions concerning the use of an anesthetic in a hemorrhoidal drug product do not make allowance for the internal use of suppositories and ointments for the treatment of skin in the anal canal below the mucocutaneous junction. The comment urged that the Panel's definitions of "external" and "internal" and its recommended labeling be clarified to promote correct consumer use of these products.

The Panel used the term "external," but not the word "internal," preferring "intrarectal" instead. The Panel consistently referred to the skin of the perianal area and the skin of the anal canal up to the mucocutaneous junction as external, and to the mucous membranes above the mucocutaneous junction, i.e., in the rectum, as intrarectal. It is apparent that, in the Panel's view, the point of distinction between "external" and "internal" use was the mucocutaneous junction. The agency believes that the Panel's definition of external use and intrarectal use are appropriate. Therefore, the agency is proposing those definitions in this tentative final monograph.

The comment is correct in stating that the Panel did not recommend labeling for the intrarectal application of suppositories and ointments containing a local anesthetic to relieve pain stemming from irritation outside the rectum (i.e., in the anal canal below the mucocutaneous junction and perianal area). Although the comment contends that such an intrarectal application would be effective because of liquefaction of the product and subsequent seepage through the anal canal, the Panel considered seepage only within the context of an incontinent anal sphincter and not within the context that an incontinent anal sphincter would provide a means to relieve external symptoms on the skin of the perianal area and the anal canal. Rather, the Panel considered intrarectal application only for local effect inside the rectum. The comment provided no data to alter the Panel's recommendations, and the agency believes that the intrarectal application of a suppository or ointment is not an appropriate means to alleviate external symptoms through liquefaction and seepage. Further, the agency disagrees with the comment's argument that the Panel's recommended warnings will result in a great deal of unalleviated consumer "hemorrhoidal discomfort." Most of the ingredients included in the tentative final monograph, but not local anesthetics, may be used intrarectally to alleviate discomfort. The Panel's recommended warnings would only apply to the small number of OTC anorectal drug products to be used externally only. Accordingly, the general warning for any anorectal ingredient intended for external use, as recommended by the Panel in § 346.50(c)(6), is being included in this tentative final monograph, but has been redesignated as § 346.50(c)(4). However, the warning recommended by the Panel in § 346.52(c)(2) for products containing local anesthetics for external use is not being proposed in this tentative final monograph because it is repetitive of the warning proposed § 346.50(c)(4).

47. One comment disagreed with the warning recommended by the Panel in § 346.54(c), "Do not use this product if you have heart disease, high blood pressure, hyperthyroidism, diabetes, difficulty in urination, or are taking tranquilizers or nerve pills." The comment stated that this warning would virtually eliminate the use of OTC anorectal drug products containing vasoconstrictor active ingredients by a large number of persons over 35 years of age who self-treat hemorrhoidal disorders. The comment recommended substituting a cautionary statement in place of the phrase "do not use."

The agency has reviewed the Panel's general discussion of vasoconstrictors (45 FR 35620) and the warning recommended in § 346.54(c) and has compared this warning with the warnings proposed for vasoconstrictor active ingredients in the final monograph for OTC bronchodilator drug products, published in the **Federal Register** of October 2, 1986 (51 FR 35326), and in the tentative final monograph for OTC nasal decongestant drug products, published in the **Federal Register** of January 15, 1985 (50 FR 2220). The Panel stated that a concomitant effect occurs on receptors in the heart and lungs when vasoconstrictors are applied to receptors in the anorectal area (45 FR 35620). Because of these potentially serious side effects and because useful effects are achieved with minimum quantities of vasoconstrictors, the Panel recommended that the safe OTC anorectal dosages of vasoconstrictors be equivalent to safe intravenous dosages. The Panel stated that when vasoconstrictors are used in these doses for local effect, undesirable systemic effects can be avoided (45 FR 35621).

However, the Panel recommended the warning in § 346.54(c) to alert consumers to undesirable side effects that can occur if systemic absorption occurs from either external or intrarectal application. These side effects can include elevated blood pressure, cardiac arrhythmia or irregular heart rate, central nervous system disturbance or nervousness, tremor, sleeplessness, and aggravation of symptoms of hyperthyroidism. Prolonged use of excessive dosage can also lead to anxiety or paranoia (45 FR 35621).

The agency concludes that vasoconstrictors used in the anorectal area, if absorbed, could cause the same undesirable systemic effects as vasoconstrictors used as bronchodilators and nasal decongestants, but that significant absorption is unlikely to occur when vasoconstrictors are used externally on intact skin for a short time. However, because the skin of the anorectal area is

usually abraded, and swollen hemorrhoids may be present, there is an increased potential for systemic absorption of vasoconstrictors used externally.

Therefore, the agency agrees with the Panel that a warning for anorectal vasoconstrictors is appropriate for both external and intrarectal use; however, the agency is proposing an expanded warning in this tentative final monograph to be consistent with the warnings required for these drugs when used as bronchodilators and nasal decongestants. The revised warning reads as follows for externally applied anorectal vasoconstrictors: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor." In addition, the phrase "* * * or are taking tranquilizers or nerve pills" recommended by the Panel in § 346.54(c) is changed to the following standard drug interaction precaution that appears in the bronchodilator final monograph for drug products containing ephedrine and epinephrine and in the nasal decongestant tentative final monograph for drug products containing phenylephrine hydrochloride for oral use: "Do not use this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

Because of the seriousness of the side effects that may occur if vasoconstrictors are systemically absorbed, cautionary language, as suggested by the comment, would not be adequate to alert consumers. However, the agency has added to the warnings the qualifying phrases "unless directed by a doctor," "consult your doctor," and "without first consulting your doctor" to make it clear that consumers to whom the warnings are directed may not need to completely forgo the use of these products, but may be able to use them under the advice or supervision of a doctor. Based on the bronchodilator final monograph, the agency is proposing the following additional warning for anorectal drug products containing ephedrine: "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

48. One comment stated that the warnings recommended for all anorectal drug products in § 346.50(c) (1), (2), and (3) should not apply to petrolatum. Concerning the warning in § 346.50(c)(1), "If symptoms do not improve, do not use this product for more than seven days and consult a physician," the comment argued that the use of this ingredient for more than 7 days would not be hazardous per se because petrolatum is remarkably safe and does not cause any allergic reaction or skin irritation.

The comment stated that the warning in § 346.50(c)(2), "Do not exceed the recommended daily dosage except under the advice and supervision of a physician," would clutter the label without benefit to the consumer because petrolatum can be applied liberally to the affected anorectal area without hazard to the patient.

Concerning the warning in § 346.50(c)(3), "If itching persists for more than 7 days, consult a physician," the comment argued that 7 days is an arbitrary limitation because the dividing line between acute and chronic conditions has not been shown to be 7 days. The comment added that including the warnings in § 346.50(c) (1) and (3) would be redundant. The comment stated that the following warning is appropriate for petrolatum: "If symptoms continue to occur or increase, consult physician."

The warning recommended by the Panel in § 346.50(c)(1) is a general warning for all anorectal drug products and is intended to inform the consumer of the period of time that is reasonable to allow for symptoms of anorectal disorders to begin to show improvement or to clear. As discussed in comment 44 above, the agency is proposing that § 346.50(c)(1) be revised in this tentative final monograph to read as follows: "If condition worsens or does not improve within 7 days, consult a doctor." The agency concludes that this warning should be required for all anorectal drugs, including petrolatum, in order to provide the consumer with appropriate limitation-of-use information for OTC anorectal drug products. The warning suggested by the comment did not include this information.

The warning in § 346.50(c)(2) is also a general warning for all anorectal drug products. In the tentative final monograph for OTC skin protectant drug products, published in the **Federal Register** of February 15, 1983 (48 FR 6820), the agency proposed that the directions for use for petrolatum state, "Apply liberally as often as necessary." Because a warning such as in § 346.50(c)(2) is not required for petrolatum in the skin protectant tentative final monograph, the agency is proposing that petrolatum be exempt from this warning in this tentative final monograph.

The general warning recommended by the Panel in § 346.50(c)(3) for all anorectal drug products specifically addresses the condition of itching. As revised, the warning in § 346.50(c)(1), which addresses all conditions, makes the warning in § 346.50(c)(3) repetitive and unnecessary and it is not included in this tentative final monograph.

49. One comment stated that the directions for anorectal drug products recommended by the Panel in § 346.50(d) should not be listed separately for external and intrarectal use. The comment contended that the directions would be understood without putting them under separate headings, and that repeating each set of directions "for all products" is redundant and contributes to label clutter.

The agency agrees with the comment. As the Panel noted, many anorectal products may be used externally as well as intrarectally. The agency acknowledges this fact and has developed directions for use in this tentative final monograph that take into account the dual use of many of these products. However, there is certain additional directions information that applies to intrarectal use only, e.g., use of a special applicator to apply the product into the rectum. In those cases, the agency believes that a special heading indicating that these directions apply to intrarectal use is appropriate.

50. Four comments opposed, and one comment favored, the following directions recommended by the Panel in § 346.50(d)(2) for all anorectal drug products: "When practical wash the anorectal area with mild soap and warm water and rinse off all soap before application of this product." The comments contended that the statement is impractical and inappropriate and that it is not always convenient or even possible for the consumer to wash the anorectal area, especially after each bowel movement or when away from home. The comments argued that the Panel did not present evidence that washing is safe and effective and that washing might not serve a useful purpose, but instead might aggravate painful burning and itching disorders. Two comments further stated that cleansing pads are a more comfortable alternative if soap and water irritate sensitive or broken skin. The comment in favor of these directions commended the Panel for emphasizing good anal hygiene when treating anorectal disorders.

The Panel was concerned about the importance of anal hygiene and stated that washing the anorectal area daily and after each bowel movement with

soap and water and then carefully removing the soap greatly aids in the relief of anorectal symptoms and may prevent recurrence of perianal itching (45 FR 35584). The Panel also emphasized that, to avoid further irritation, the skin of the perianal area should be patted or blotted rather than rubbed dry.

The agency agrees with the comments' suggestion that cleansing pads are a suitable alternative to washing with soap and water, but recognizes that cleansing pads may not always be available. Accordingly, the directions proposed in this tentative final monograph, which appear in § 346.50(d)(1), have been revised for clarity. In addition, the directions have also been revised because the agency is not including the Panel's recommended warning in § 346.50(c)(7)(iii) for certain products for intrarectal use, "Do not use this product in children under 12 years of age except under the advice and supervision of a physician." Rather, the directions in § 346.50(d)(i) of this tentative final monograph have been revised to state clearly that a doctor should be consulted before using any anorectal drug product in children under 12 years of age to be more consistent with the Panel's general discussion on pediatric dosages in which the Panel stated that most anorectal disorders in children are brought to a physician for evaluation and treatment (45 FR 35579). In light of the revised directions, the agency believes that the warning recommended by the Panel is repetitious and unnecessary. The revised directions are as follows: "*Adults:* "When practical, cleanse the affected area" (select one or both of the following: "with mild soap and warm water and rinse thoroughly" or "by patting or blotting with an appropriate cleansing pad"). "Gently dry by patting or blotting with toilet tissue or a soft cloth before application of this product." [Other appropriate directions may be inserted here.] "Children under 12 years of age: consult a doctor."

51. One comment urged deletion of the phrase "or as directed by a physician" from the directions for petrolatum recommended by the Panel in § 346.56(d). The comment contended that the phrase is unnecessary and irrelevant for petrolatum because petrolatum is not usually prescribed by physicians, and therefore its use is rarely directed or supervised by a physician. The comment further contended that in the unusual case when a physician does direct the use of petrolatum, the physician's directions to the patient would take precedence over the label directions without the need for a statement to that effect on the label.

The agency agrees with the comment that the phrase "or as directed by a physician" is unnecessary in the directions for petrolatum. In addition, the agency believes that this phrase is unnecessary for any OTC anorectal drug product and is not including it in this tentative final monograph. Deleting this phrase makes the directions for all anorectal drug products consistent with the directions for other OTC topically applied ingredients contained in other tentative final monographs, i.e., skin protectants and external analgesics. (See comment 28 above.)

52. One comment objected to several of the Panel's Category II labeling recommendations as being excessive and unnecessary. The comment disagreed with the Panel's conclusion at 45 FR 35602 that the labeling claims "simple anorectal irritation," "anorectal disorders," and "simple inflammatory rectal conditions" are too general and contended that these terms are intended to encourage OTC hemorrhoidal drug use only in cases in which medical supervision is unnecessary. The comment added that labeling a hemorrhoidal product for a "simple anorectal condition" may be the best method of encouraging consumers to obtain medical advice if the condition persists or becomes a "complicated" anorectal condition.

The agency agrees with the Panel that labeling claims such as "simple anorectal irritation," "anorectal disorders," and "simple inflammatory rectal conditions" are too general or unclear if used alone (45 FR 35602). Further, the agency finds that such labeling claims, when used alone, could imply that OTC anorectal drug products treat diseases or conditions rather than relieve symptoms and, therefore, should remain in Category II. However, when these terms or similar terms are used with additional language describing the relief of associated symptoms, e.g., itching, discomfort, etc., the resulting labeling claims clearly describe that OTC anorectal drugs are primarily for the relief of symptoms and not the treatment of disease. Therefore, the agency is not proposing that the terms recommended by the comment be used alone as labeling for anorectal drug products. However, these terms or similar terms when used with additional language are included in the labeling proposed in § 346.50(b). (See comment 40 above.)

53. One comment objected to the Panel's criticism of labeling claims that may cause the consumer to believe that certain hemorrhoidal drug products are superior to other available products for any of a number of reasons (45 FR 35602) and what the comment described as the Panel's impression that one hemorrhoidal drug product is as good as another.

The Panel gave the following examples of labeling that may cause the consumer to believe that certain products are superior to other available products: "Contains no narcotic, anesthetic, or habit forming ingredients," "nonnarcotic," "without the use of narcotics," or "contains no stinging, smarting astringents" (45 FR 35602). The Panel stated that these claims clearly imply a stronger or more effective product, greater safety, and that other products are narcotics, anesthetics, or astringents and are harmful without any evidence that this is so. The agency has reviewed currently marketed products and finds no known marketed OTC anorectal drug products that contain narcotics. Therefore, the agency believes it would be inappropriate for manufacturers to state in the labeling of these products that the product "contains no narcotic." However, because anesthetics are present in some OTC anorectal products, manufacturers could state in their labeling, if they wish, that the product "contains no anesthetic." The agency is not aware of any data that show that astringents incorporated into an ointment or suppository base cause stinging and smarting in the anorectal area and, thus, believes that the statement "contains no stinging, smarting astringents" would be inappropriate for anorectal drug products.

N. Comments on Testing Guidelines.

54. A number of comments disagreed with parts of the Panel's testing guideline requirements, e.g., that the pharmacologic action of ingredients must always be demonstrated in the anorectal area, that clinical relief of symptoms must be correlated with pharmacologic activity, and that testing must be accomplished within 7 days. The comments also criticized the criteria for selection of patients with anorectal disease, the use of a product's vehicle as the control, double-blind studies, and the dose and frequency limitations. Two comments suggested that the Panel's testing requirements for anorectal drug products at 45 FR 35594 are more rigorous than for other drug entities, while another comment stated that the proposed requirements would limit manufacturers and independent testing organizations to inappropriate and

impossible testing methods. Several comments supported the Panel's minority opinion that extrapolation of data from tests performed in other areas of the body to the anorectal area is allowable (45 FR 35608 and 35652).

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A.2. below—*Testing of Category II and Category III conditions.*)

55. A number of comments objected to the Panel's recommendation of final formulation testing (bioavailability) for moving Category III anorectal drug products to Category I. There were no comments supporting the Panel's views. Some comments stated that adopting this requirement as part of the final rule would violate the Panel's charter, which was to review data on OTC ingredients and combinations, to make recommendations on their safety and efficacy, and to avoid a product-by-product review. Several comments cited 21 CFR 320.22(b)(2) as providing for a waiver of in vivo bioavailability requirements for topically applied preparations intended for local therapeutic effect. The comments also stated that none of the anorectal ingredients reviewed by the Panel has been cited as having bioavailability problems.

Two of the comments contended that consideration of the bioavailability of anorectal drug products is irrelevant, and that the Panel had not supported the final formulation testing recommendation with any documentation. One comment from a biopharmaceutics expert who had written a letter in 1975 (Ref. 1) that was reviewed and quoted by the Panel to support its conclusion to require final formulation testing for anorectal drug products (45 FR 35586 to 35588) contended that the Panel misconstrued the content of the letter. The comment stated that final formulation testing is not necessary for safety because there would be no significant risk to the user even if any of the Category I and III anorectal active ingredients were 100 percent bioavailable systemically. Another comment agreed with the Panel's minority report regarding final formulation testing (45 FR 35608, 35609, and 35652) and stated that "final formulation testing would be wasteful, a threat to * * * viability as a hemorrhoidal drug marketer, and, ultimately, a financial detriment to consumers."

FDA does not agree with the comment concerning the 1975 letter cited in the Panel's report. After reviewing the Panel's discussion of its reasons for recommending final formulation testing (45 FR 35586 to 35588), it is evident that the Panel did not quote from the letter discussed in the summary above, nor does it appear that the letter was cited for the proposition mentioned in the comment.

Although the Panel stated that final formulation testing of all ingredients and combinations could not be avoided in its testing guidelines for placing Category III ingredients and labeling in Category I (45 FR 35594 to 35598), the Panel also stated, and the agency concurs, that the use of a questionnaire, photography, and physician evaluation would be adequate to demonstrate statistically significant symptomatic improvement and would be acceptable for proof of effectiveness for claims of symptomatic relief of burning, pain, itch, swelling (as in hemorrhoids and/or hemorrhoidal tissue) and discomfort due to these symptoms.

While it is not clear whether the Panel intended testing of all products, including formulations containing Category I ingredients, FDA agrees with the comments that final formulation testing should not be required for anorectal drug products because the products are topically applied and because, to date, there has been no demonstrated bioavailability problem with any of the products at issue. The in vivo waiver provision of § 320.22(b)(2) for topically applied products reflects the fact that certain topically applied products, that are applied directly to the site of drug action, are less prone to bioavailability problems than are some other drugs and, accordingly, their bioavailability may, in some instances, be determined by means other than in vivo product testing. With regard to the products subject to this monograph, FDA will not require in vivo bioavailability testing, but will address product bioavailability in the context of the monograph requirements of (1) appropriate vehicles and other inactive ingredients and (2) compliance with appropriate good manufacturing practices.

Accordingly, the agency will not require final formulation testing of anorectal drug products covered by a final monograph. Category I anorectal active ingredients may be formulated in appropriate vehicles without additional testing, provided the product is manufactured according to the regulations for the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR Part 211). Manufacturers should be aware that the newness of a dosage, or method * * * of administration or application, or other condition of use * * * may affect the "newness" of a drug. (See 21 CFR 310.(h)(5).)

Reference

(1) Letter to J. K. Jones from S. Riegelman, March 13, 1975, OTC Volume 120051.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions.

1. Summary of ingredient categories.

The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made the following changes in the categorization of anorectal active ingredients recommended by the Panel.

Because final formulation testing is not being proposed in this tentative final monograph, benzyl alcohol, dibucaine, dibucaine hydrochloride, dyclonine hydrochloride, epinephrine, lidocaine, tetracaine, and tetracaine hydrochloride have been reclassified from Category III to Category I for external use. (See comment 55 above.) However, these ingredients remain in Category III for intrarectal use because of insufficient data to establish safety and/or effectiveness for this use. Diperodon has been reclassified from Category II to Category III for external use while remaining in Category III for intrarectal use. (See comment 13 above.)

For the convenience of the reader, the following tables are included as a summary of the categorization of anorectal active ingredients by the Panel and the proposed classification by the agency:

Anorectal active ingredients	Panel	Agency [(e) = external use; (i) = intrarectal use]
Local anesthetics		
Benzocaine	I(e),III(i)	I(e),III(i)
Benzyl alcohol	III(e,i)	I(e),III(i)
Dibucaine	III(e,i)	I(e),III(i)
Dibucaine hydrochloride	III(e,i)	I(e),III(i)
Diperodon	II(e),III(i)	I(e),III(i)
Dyclonine hydrochloride	III(e,i)	I(e),III(i)
Lidocaine	III(e,i)	I(e),III(i)
Phenacaine hydrochloride	II(e,i)	II(e,i)
Pramoxine hydrochloride	I(e),III(i)	I(e),III(i)
Tetracaine	III(e,i)	I(e),III(i)
Tetracaine hydrochloride	III(e,i)	I(e),III(i)
Vasoconstrictors		
Ephedrine sulfate	I(e,i)	I(e,i)
Epinephrine	III(e,i)	I(e),III(i)
Epinephrine hydrochloride	I(e),II(i)	I(e),II(i)
Epinephrine undecylenate	III(e),II(i)	III(e),II(i)
Phenylephrine hydrochloride	I(e,i)	I(e,i)
Protectants		
Aluminum hydroxide gel	I(e,i)	I(e,i)
Bismuth oxide	III(e,i)	III(e,i)
Bismuth subcarbonate	III(e,i)	III(e,i)
Bismuth subgallate	III(e,i)	III(e,i)
Bismuth subnitrate	II(e,i)	II(e,i)
Calamine [1]	I(e,i)	I(e,i)
Cocoa butter	I(e,i)	I(e,i)
Cod liver oil [1]	I(e,i)	I(e,i)
Glycerin [2]	I(e)	I(e)
Kaolin	I(e,i)	I(e,i)
Lanolin	I(e,i)	I(e,i)
Lanolin alcohols [3]	I(e,i)	III(e,i)
Mineral oil	I(e,i)	I(e,i)
Petrolatum	Not reviewed	I(e,i)
Shark liver oil [1]	I(e,i)	I(e,i)
Topical starch [4]	I(e,i)	I(e,i)
White petrolatum	I(e,i)	I(e,i)
Zinc oxide [1]	I(e,i)	I(e,i)
Counterirritants		
Camphor (greater than 3 to 11 percent)	II(e,i)	II(e,i)
Hydrastis	II(e,i)	II(e,i)
Juniper tar (1 to 5 percent)	III(e,i)	N/A [5]
Menthol (1.25 to 16 percent)	II(e,i)	II(e,i)
Turpentine oil (rectified) (6 to 50 percent)	II(e,i)	II(e,i)
Astringents		
Calamine	I(e,i)	I(e,i)
Tannic acid	II(e,i)	II(e,i)
Hamamelis water, NF XI [2, 6]	I(e)	I(e)
Zinc oxide	I(e,i)	I(e,i)
Wound-healing agents		
Cholecalciferol [7]	III(e,i)	III(e,i)
Cod liver oil	III(e,i)	III(e,i)
Live yeast cell derivative	III(e,i)	III(e,i)
Peruvian balsam	III(e,i)	III(e,i)
Shark liver oil	III(e,i)	III(e,i)
Vitamin A	III(e,i)	III(e,i)
Antiseptics		
Boric acid	II(e,i)	II(e,i)
Boroglycerin	II(e,i)	II(e,i)
Hydrastis	II(e,i)	II(e,i)
Phenol	II(e,i)	II(e,i)
Resorcinol	III(e),II(i)	III(e),II(i)
Sodium salicylic acid phenolate	II(e,i)	II(e,i)
Keratolytics		
Alcloxa [2]	I(e)	I(e)
Resorcinol	I(e),II(i)	I(e),II(i)
Precipitated sulfur	III(e),II(i)	III(e),II(i)
Sublimed sulfur	III(e),II(i)	III(e),II(i)
Anticholinergics		
Atropine	II(e,i)	II(e,i)
Belladonna extract	II(e,i)	II(e,i)
Analgesics, anesthetics, and antipruritics		
Camphor (0.1 to 3 percent)	N/A	I(e)
Juniper tar (1 to 5 percent)	N/A	I(e)
Menthol (0.1 to 1 percent)	N/A	I(e)
Miscellaneous		
Collinsonia extract	II(e,i)	II(e,i)
E.coli vaccines	II(e,i)	II(e,i)
Hydrocortisone	N/A	Ext. Anal.[8]
Hydrocortisone acetate	N/A	Ext. Anal.[8]

Anorectal active ingredients	Panel	Agency [(e) = external use; (i)=intrarectal use]
Lappa extract	II(e,i)	II(e,i)
Leptandra extract	II(e,i)	II(e,i)
Mullein	II(e,i)	II(e,i)

[1] For use only in combination and not as single ingredients. (See comment 30 above.)
[2] Not categorized for intrarectal use.
[3] "Wool alcohols" was the name designated by the Panel for this ingredient. "Lanolin alcohols" is the official title of this ingredient in the "United States Pharmacopeia XXI—National Formulary XVI."
[4] "Starch" was the name designated by the Panel for this ingredient. "Topical starch" is the official title of this ingredient in the "United States Pharmacopeia XXI—National Formulary XVI."
[5] Juniper tar was redesigned an "analgesic, anesthetic, and antipruritic" ingredient. (See Part II.B.6 below—*Summary of the Agency's Changes in the Panel's Recommendations.*)
[6] "Witch hazel water" was the name designated by the Panel for this ingredient. "Hamamelis Water" was last recognized as the official title of this ingredient in National Formulary XI, and the agency has determined that this is the appropriate name for this ingredient.
[7] "Vitamin D" was the name designated by the Panel for this ingredient. "Cholecalciferol" is the official title of this ingredient in the "United States Pharmacopeia XXI—National Formulary XVI."
[8] Hydrocortisone and hydrocortisone acetate were not reviewed by the Panel. These ingredients are being addressed in the rulemaking for OTC external analgesic drug products. (See comment 25 above.)

2. Testing of Category II and Category III conditions.

The Panel recommended testing guidelines for anorectal drug products (45 FR 35594 to 35598). The agency's position regarding these testing guidelines and regarding final formulation testing is discussed in comments 54 and 55 above. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any anorectal ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The agency is proposing dibucaine and dibucaine hydrochloride as Category I anorectal local anesthetics for external use in a concentration range of 0.25 to 1 percent for use up to 3 or 4 times daily. (See comment 12 above.)

The agency is also proposing the following anorectal ingredients as Category I for external use. (See part II. paragraph A. 1. above—*Summary of ingredient categories.*) The concentrations in this tentative final monograph are the equivalent of the dosages recommended by the Panel for a 2-g or a 2-mL dosage unit.

(a) Benzyl alcohol 1 to 4 percent.

(b) Dyclonine hydrochloride 0.5 to 1 percent.

(c) Lidocaine 2 to 5 percent.

(d) Tetracaine and tetracaine hydrochloride 0.5 to 1 percent.

(e) Epinephrine 0.005 to 0.01 percent.

2. In its recommended monograph, the Panel stated the amounts of the vasoconstrictor active ingredients identified in § 346.12 in terms of a given weight per 2-g or 2-mL dosage unit. The agency proposes that the ingredients be expressed in terms of percentage concentration to be consistent with the manner of stating other ingredients in this tentative final monograph. Accordingly, the vasoconstrictor active ingredients in § 346.12 of this tentative final monograph are expressed as follows:

(a) Ephedrine sulfate 0.1 to 1.25 percent.

(b) Epinephrine 0.005 to 0.01 percent.

(c) Epinephrine hydrochloride 0.005 to 0.01 percent

(d) Phenylephrine hydrochloride 0.25 percent.

The agency is aware that in the Panel's report (45 FR 35625) the statement is made that "a 0.5 mg dose of phenylephrine hydrochloride in a 2 mL dosage unit is equal to the amount of phenylephrine used safely and effectively in producing nasal decongestion, as discussed in the September 9, 1976 document at page 38399." The statement is incorrect and should have read "a 5-mg dose." Such a dose represents a concentration of 0.25 percent phenylephrine.

3. The agency is reclassifing lanolin alcohols from Category I to Category III as protectants in OTC anorectal drug products. Lanolin alcohols were not contained in any products submitted to the Panel for review, and the agency has no information on currently marketed anorectal drug products that contain these ingredients or on their appropriate concentration for anorectal protectant use. Such information is needed before lanolin alcohols can be considered generally recognized as safe and effective as anorectal protectants, and the agency invites public comment and the submission of data.

4. The agency is not requiring the final formulation testing of combination drug products recommended by the Panel. Accordingly, combinations of Category I ingredients from up to three different therapeutic categories that were placed in Category III by the Panel are reclassified in Category I. (See comment 31 above.)

5. The agency is proposing in § 346.14(b) in this tentative final monograph that calamine, cod liver oil, shark liver oil, and zinc oxide not be used alone but only in combination with other protectants to provide at least 50 percent by weight of the final product. Section 346.22 of the Panel's recommended monograph has been redesignated as § 346.22(a) and has been expanded to clarify that any two, three, or four protectants identified in § 346.14 may be combined, provided that any ingredient identified in § 346.14 is included at a level that contributes at least 12.5 percent by weight (e.g., 0.25 g of a 2-g dosage unit) and provided that if any ingredient identified in § 346.14(b) is present in the combination, it must not exceed the concentration limit specified in § 346.14(b). In addition, the combined percentage by weight of all protectants in the combination must be at least 50 percent of the final product (e.g., 1-g of a 2-g dosage unit). New § 346.22(o) provides that the amount of zinc oxide in a combination may not exceed 25 percent by weight per dosage unit. (See

comment 30 above.) In addition, on its own initiative, the agency is expanding the list of protectant active ingredients in § 346.14 to include petrolatum as well as white petrolatum. Although the use of white petrolatum in lieu of petrolatum results in a more aesthetically pleasing anorectal ointment, the use of white petrolatum is not medically necessary.

6. The agency is redesignating several ingredients that the Panel classified as "counterirritants" to be "analgesic, anesthetic, and antipruritic" ingredients in this rulemaking. The Panel classified the ingredients camphor (1.6 to 7 percent), hydrastis (no concentration given), juniper tar (1 to 5 percent), menthol (0.25 to 1 percent), and turpentine oil (no concentration given) as counterirritants (45 FR 35640 to 35645). The Topical Analgesic Panel also reviewed and classified camphor (0.1 to 3 percent), juniper tar (1 to 5 percent), and menthol (0.1 to 1 percent) as analgesic, anesthetic, and antipruritic active ingredients (44 FR 69865) and camphor (3 to 11 percent), menthol (1.25 to 16 percent), and turpentine oil (6 to 50 percent) as counterirritant ingredients (44 FR 69864 to 69865). The agency agreed with that Panel's classifications in the tentative final monograph for OTC external analgesic drug products (48 FR 5852; February 8, 1983), and further clarified that menthol at a concentration of 0.1 to 1 percent was an analgesic, anesthetic, or antipruritic and at a concentration of 1.25 to 16 percent was a counterirritant. (See comment 6 at 48 FR 5855.)

The Anorectal Panel classified menthol at a concentration of 0.25 to 1 percent in aqueous solution as a counterirritant for the temporary relief of itching in the anorectal area.

Based on the agency's findings in the tentative final monograph for OTC external analgesic drug products and to promote consistency between the rulemakings for anorectal and external analgesic drug products, the agency is proposing to redesignate menthol below 1 percent as an analgesic, anesthetic, and antipruritic ingredient rather than as a counterirritant in the anorectal rulemaking and to revise its Category I concentration from 0.25 to 1 percent to 0.1 to 1 percent. Likewise, camphor 0.1 to 3 percent and juniper tar 1 to 5 percent will be redesignated as analgesic, anesthetic, and antipruritic ingredients in the anorectal rulemaking. The Anorectal Panel did not classify these ingredients for these uses. However, because these ingredients are indicated for pain and itching of minor skin irritations when labeled as an external analgesic and for itching and discomfort when labeled for anorectal/hemorrhoidal use, the agency has determined that menthol, camphor, and juniper tar at the above concentrations should be listed as Category I analgesic, anesthetic, and antipruritic ingredients in the anorectal tentative final monograph.

Camphor exceeding 3 percent to 11 percent, menthol 1.25 to 16 percent, and turpentine oil 6 to 50 percent are designated as counterirritants in the anorectal rulemaking. Because the Anorectal Panel classified camphor and turpentine oil in Category II as counterirritants for anorectal use, they are not being included in this tentative final monograph. Likewise, the Panel did not propose Category I status for menthol above 1 percent as a counterirritant; therefore, it also is not being included in this tentative final monograph as a counterirritant. This approach is consistent with the labeling of counterirritants in the external analgesic tentative final monograph because those products are used to relieve aches and pains of muscles and joints associated with backaches, arthritis, etc., and not to relieve itching and discomfort of minor skin irritations. Hydrastis also remains in Category II as a counterirritant in OTC anorectal drug products.

The agency is adding the definitions of "analgesic, anesthetic" and "antipruritic" to this tentative final monograph to be consistent with those definitions as proposed in the tentative final monograph for OTC external analgesic drug products. (See the **Federal Register** of February 8, 1983; 48 FR 5852.) In addition, the agency is not including the definition of counterirritant in this tentative final monograph.

7. The agency is redesignating Subpart D as Subpart C and is placing the labeling sections of the tentative final monograph in Subpart C. To improve clarity and to eliminate duplicative words and phrases, the agency has shortened and simplified the general indications and the indications recommended by the Panel for different therapeutic categories. (See comment 40 above.) In some cases, the agency has eliminated indications from the different therapeutic categories when the same or very similar indications were already part of the general indications.

8. The agency is proposing that the term "hemorrhoidal" be allowed to appear alone or in parentheses next to the term "anorectal" as the statement of identity for all OTC anorectal drug products. (See comment 38 above.)

9. The agency is proposing in § 346.50(b) that certain labeling statements may be combined in the labeling of anorectal combination drug products. The agency is proposing in § 346.54 that indications, warnings, and directions applicable to each active ingredient of the combination product may be combined, respectively, to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

10. Cosmetic-related terms, such as "bland," "soothing," "lubrication," "lubricates," "* * * soften and lubricate dry * * *" are not included in the labeling for protectants in § 346.50(b)(iii) of this tentative final monograph. The agency's policy on such labeling was stated in the tentative final monograph for OTC skin protectant drug products. (See 48 FR 6827, comment 22.)

11. In § 346.52(c)(1), § 346.56(c)(2), § 346.58(c), and § 346.62(c)(1)(i), the Panel recommended the use of the signal word "Caution" in labeling for which the heading "Warnings" was also recommended. The agency notes that historically there has not been a consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in § 369.20 and § 369.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems.

12. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulation will give manufacturers the option of using either the word "physician" or the

word "doctor." This tentative final monograph includes that option.

13. The Panel's recommendations concerning a "box border" and various graphic effects for highlighting warnings on anorectal drug products are not included in § 346.50(c). (See comment 42 above.)

14. The agency is revising the general warning in § 346.50(c)(1) to read as follows: "If condition worsens or does not improve within 7 days, consult a doctor."

The agency is not including the general warning recommended by the Panel in § 346.50(c)(3), "If itching persists for more than 7 days, consult a physician," because the revised warning in proposed § 346.50(c)(1) addresses all conditions, not just itching. (See comment 48 above.)

The agency is proposing in § 346.56(c)(3) that petrolatum be exempt from the warning in § 346.50(c)(2), "Do not exceed the recommended daily dosage unless directed by a doctor."

15. The agency is revising the warning recommended by the Panel in § 346.50(c)(7)(ii) for clarity, to read as follows: "Do not use this product with an applicator if the introduction of the applicator into the rectum causes additional pain. Consult a doctor promptly." (See comment 45 above.)

16. The agency is not including the Panel's recommended warning in § 346.52(c)(2) for products containing local anesthetics for external use because it would be repetitive of the general warning proposed in § 346.50(c)(4). (See comment 46 above.)

17. The agency is proposing that anorectal vasoconstrictors bear the same warnings for anorectal use as for bronchodilator and nasal decongestant use. These warnings include the following: "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor"; and the drug interaction precaution "Do not use this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor." The agency is proposing the following additional warning for ephedrine sulfate: "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor." (See comment 47 above.)

18. The Panel's recommended warning and directions for use for lanolin (wool) alcohols (§ 346.56 (c)(2) and (d)(12)) are not included in this tentative monograph because lanolin alcohols are being reclassified from Category I to Category III as anorectal protectants. (See part II. paragraph B.3. above.)

19. The agency is not accepting the Panel's recommendation to have complete and separate directions for products labeled for both external and intrarectal use. Rather, the agency has developed directions for use that take into account the dual use of these products. (See comment 49 above.)

20. The Panel's recommended directions in § 346.50(d)(2) (redesignated as § 346.50(d)(1)) has been revised for clarity as follows: "*Adults*: "When practical, cleanse the affected area" (select one or both of the following: "with mild soap and warm water and rinse thoroughly" or "by patting or blotting with an appropriate cleansing pad"). "Gently dry by patting or blotting with toilet tissue or a soft cloth before application of this product." [Other appropriate directions may be inserted here.] "Children under 12 years of age: consult a doctor." (See comment 50 above.)

21. The agency is not proposing the phrase "or as directed by a physician" in the directions for any anorectal product in this tentative final monograph. The directions for use of petrolatum have been revised to be consistent with the directions in the skin protectant tentative final monograph, so that proposed § 346.56(d)(6) reads "Apply liberally as often as necessary." (See comments 28 and 51 above.)

22. A claim for hydrocortisone and hydrocortisone acetate for the temporary relief of anal itching is already included in the tentative final monograph for OTC external analgesic drug products. In a future issue of the **Federal Register**, the agency will amend that tentative final monograph so that external analgesic drug products containing hydrocortisone or hydrocortisone acetate and bearing claims for the relief of "anal itching" would also bear the appropriate warnings and directions for anorectal drug products. (See comment 25 above.)

The agency is proposing to remove the existing labeling requirements of § 310.201(a)(23)(v)(b) (21 CFR 310.201(a)(23)(v)(*b*)) relating to dyclonine hydrochloride at the time that a final monograph for OTC anorectal drug products becomes effective. In addition, the agency is proposing to revise § 369.20 to remove the reference to rectal preparations from the entry for "BELLADONNA PREPARATIONS * * *" and to remove the entry for "RECTAL PREPARATIONS FOR EXTERNAL USE" because these entries will be superseded by a final monograph for OTC anorectal drug products.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC anorectal drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96–354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC anorectal drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC anorectal drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC anorectal drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on anorectal drug products, a period of 120 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has carefully considered the potential environmental effects of that action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not

required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday. This action was considered under FDA's final rule implementing the National Environmental Policy Act (21 CFR Part 25).

Interested persons may, on or before December 13, 1988 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 13, 1988. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before August 15, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before October 15, 1989. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on October 15, 1989. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR

21 CFR Part 310

Administrative practice and procedure, Drugs, New drugs, Prescription exemption, Reporting and recordkeeping requirements.

21 CFR Part 346

Anorectal drug products, Labeling, Over-the-counter drugs.

21 CFR Part 369

Labeling, Over-the-counter drugs, Warning and caution statements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR Part 310 is revised to read as follows:

Authority: Secs. 502, 503, 505, 701, 52 Stat. 1051, 1052, 1053, 1055 as amended (21 U.S.C. 352, 353, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

§ 310.201 [Amended]

2. Section 310.201 *Exemption for certain drugs limited by new-drug applications to prescription sale* is amended by removing paragraph (a)(23)(v)(*b*) and reserving it.

PART 346—ANORECTAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. Part 346 is added to read as follows:

Subpart A—General Provisions.

Sec.
346.1 Scope.
346.3 Definitions.

Subpart B—Active Ingredients

346.10 Local anesthetic active ingredients.
346.12 Vasoconstrictor active ingredients.
346.14 Protectant active ingredients.
346.16 Analgesic, anesthetic, and antipruritic active ingredients.
346.18 Astringent active ingredients.
346.20 Keratolytic active ingredients.
346.22 Permitted combinations of anorectal active ingredients.

Subpart C—Labeling

346.50 Labeling of anorectal drug products.
346.52 Labeling of permitted combinations of anorectal active ingredients.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart A—General Provisions

§ 346.1 Scope.

(a) An over-the-counter anorectal drug product in a form suitable for external (topical) or intrarectal (rectal) administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1 of this chapter.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 346.3 Definitions.

As used in this part:

(a) *Analgesic, anesthetic drug.* A topically (externally) applied drug that relieves pain by depressing cutaneous sensory receptors.

(b) *Anorectal drug.* A drug that is used to relieve symptoms caused by anorectal disorders in the anal canal, perianal area, and/or the lower rectal areas.

(c) *Antipruritic drug.* A topically (externally) applied drug that relieves itching by depressing cutaneous sensory receptors.

(d) *Astringent drug.* A drug that is applied to the skin or mucous membranes for a local and limited protein coagulant effect.

(e) *External use.* Topical application of an anorectal drug product to the skin of the perianal area and/or the skin of the anal canal.

(f) *Intrarectal use.* Topical application of an anorectal drug product to the mucous membrane of the rectum.

(g) *Keratolytic drug.* A drug that causes desquamation (loosening) and debridement or sloughing of the surface cells of the epidermis.

(h) *Local anesthetic drug.* A drug that produces local disappearance of pain, burning, itching, irritation, and/or discomfort by reversibly blocking nerve conduction when applied to nerve tissue in appropriate concentrations.

(i) *Protectant drug.* A drug that provides a physical barrier, forming a protective coating over skin or mucous membranes.

(j) *Vasoconstrictor drug.* A drug that causes temporary constriction of blood vessels.

Subpart B—Active Ingredients

§ 346.10 Local anesthetic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentrations established for each ingredient:

(a) Benzocaine 5 to 20 percent.

(b) Benzyl alcohol 1 to 4 percent.

(c) Dibucaine 0.25 to 1 percent.

(d) Dibucaine hydrochloride 0.25 to 1 percent.

(e) Dyclonine hydrochloride 0.5 to 1 percent.

(f) Lidocaine 2 to 5 percent.

(g) Pramoxine hydrochloride 1 percent.

(h) Tetracaine 0.5 to 1 percent.

(i) Tetracaine hydrochloride 0.5 to 1 percent.

§ 346.12 Vasoconstrictor active ingredients.

The active ingredient of the product consists of any of the following when used within the concentrations established for each ingredient:

(a) Ephedrine sulfate 0.1 to 1.25 percent.

(b) Epinephrine 0.005 to 0.01 percent.

(c) Epinephrine hydrochloride 0.005 to 0.01 percent.

(d) Phenylephrine hydrochloride 0.25 percent.

§ 346.14 Protectant active ingredients.

(a) The following active ingredients may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product. In addition, the following active ingredients may be used in combinations in accordance with § 346.22 (a), (b), or (n).

(1) Aluminum hydroxide gel.

(2) Cocoa butter.

(3) Glycerin in a 20- to 45-percent (weight/weight) aqueous solution.

(4) Kaolin.

(5) Lanolin.

(6) Mineral oil.

(7) Petrolatum.

(8) Topical starch.

(9) White petrolatum.

(b) The following active ingredients may not be used as a sole protectant ingredient but may be used in combination with one, two, or three other protectant active ingredients in accordance with § 346.22 (a), (b), (n), and (o) and with the following limitations:

(1) Calamine not to exceed 25 percent by weight per dosage unit (based on the zinc oxide content of calamine).

(2) Cod liver oil, provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(3) Shark liver oil, provided that the product is labeled so that the amount of the product that is used in a 24-hour period represents a quantity that provides 10,000 U.S.P. units of vitamin A and 400 U.S.P. units of cholecalciferol.

(4) Zinc oxide not to exceed 25 percent by weight per dosage unit.

§ 346.16 Analgesic, anesthetic, and antipruritic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentrations established for each ingredient:

(a) Camphor 0.1 to 3 percent.

(b) Juniper tar 1 to 5 percent.

(c) Menthol 0.1 to 1 percent.

§ 346.18 Astringent active ingredients.

The active ingredient of the product consists of any of the following when used within the concentrations established for each ingredient:

(a) Calamine, within a concentration of 5 to 25 percent by weight per dosage unit (based on the zinc oxide content of calamine).

(b) Hamamelis water, NF XI, 10 to 50 percent.

(c) Zinc oxide, within a concentration of 5 to 25 percent by weight per dosage unit.

§ 346.20 Keratolytic active ingredients.

The active ingredient of the product consists of any of the following when used within the concentrations established for each ingredient:

(a) Alcloxa 0.2 to 2 percent.

(b) Resorcinol 1 to 3 percent.

§ 346.22 Permitted combinations of anorectal active ingredients.

(a) Any two, three, or four protectants identified in § 346.14 may be combined, provided that the combined percentage by weight of all protectants in the combination is at least 50 percent of the final product (e.g., 1 gram of a 2-gram dosage unit). Any protectant ingredient included in the combination must be present at a level that contributes at least 12.5 percent by weight (e.g., 0.25 gram of a 2-gram dosage unit), except cod liver oil and shark liver oil. If an ingredient in § 346.14(b) is included in the combination, it must not exceed the concentration limit specified in § 346.14(b).

(b) Any single anorectal ingredient identified in § 346.10, § 346.12, § 346.16, § 346.18, or § 346.20 may be combined with up to four protectants in accordance with paragraph (a) of this section.

(c) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12.

(d) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18.

(e) Any single local anesthetic identified in § 346.10 may be combined with any single keratolytic identified in § 346.20.

(f) Any single vasoconstrictor identified in § 346.12 may be combined with any single astringent identified in § 346.18.

(g) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18.

(h) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single keratolytic identified in § 346.20.

(i) Any single astringent identified in § 346.18 may be combined with any single keratolytic identified in § 346.20.

(j) Any single local anesthetic identified in § 346.10 may be combined with any single vasoconstrictor identified in § 346.12 and with any single astringent identified in § 346.18.

(k) Any single local anesthetic identified in § 346.10 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(l) Any single vasoconstrictor identified in § 346.12 may be combined with any single analgesic, anesthetic, and antipruritic identified in § 346.16 and with any single astringent identified in § 346.18.

(m) Any single analgesic, anesthetic, and antipruritic identified in § 346.16 may be combined with any single astringent identified in § 346.18 and with any single keratolytic identified in § 346.20.

(n) Any combination of ingredients listed in paragraphs (c) through (m) of this section may be combined with up to four protectants in accordance with paragraph (a) of this section.

(o) Any product containing calamine for use as a protectant and/or as an astringent and/or containing zinc oxide for use as a protectant and/or as an astringent may not have a total weight of zinc oxide exceeding 25 percent by weight per dosage unit.

Subpart C—Labeling

§ 346.50 Labeling of anorectal drug products.

The labeling of the product contains the following information for anorectal

ingredients identified in §§ 346.10, 346.12, 346.14, 346.16, 346.18, and 346.20, and for combinations of anorectal ingredients identified in § 346.22. Unless otherwise specified, the labeling in this subpart is applicable to anorectal drug products for both external and intrarectal use.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as "anorectal (hemorrhoidal)," "hemorrhoidal," "hemorrhoidal (anorectal) (insert dosage form, e.g., cream, lotion, or ointment)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ("For the temporary relief of," "Gives temporary relief of," or "Helps relieve the") (As an option, select one or both of the following: "local" or "anorectal") [select one or more of the following: "discomfort," "itching," or "itching and discomfort," followed by: "in the perianal area" or "associated with" (select one or more of the following: "hemorrhoids," "anorectal disorders," "inflamed hemorrhoidal tissues," "anorectal inflammation," "hemorrhoidal tissues," or "piles (hemorrhoids).")]

(2) *Additional indications.* Indications applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting indication is clear and understandable. In addition to the indication identified in paragraph (b)(1) of this section, the labeling of the product intended for external or intrarectal use may also contain the following indications, as appropriate.

(i) *For products for external use only containing any ingredient identified in § 346.10.* "For the temporary relief of" (select one or more of the following: "pain," "soreness," or "burning").

(ii) *For products containing epinephrine or epinephrine hydrochloride identified in § 346.12 (b) and (c) for external use only, and for products containing ephedrine sulfate or phenylephrine hydrochloride identified in § 346.12 (a) and (d).*

(A) "Temporarily reduces the swelling associated with" (select one of the following: "irritated hemorrhoidal tissue and other anorectal disorders" or "irritation in hemorrhoids and other anorectal disorders").

(B) "Temporarily shrinks hemorrhoidal tissue."

(iii) *For products for external use only containing glycerin identified in § 346.14(a)(3) and for products for external and/or intrarectal use containing any protectant identified in § 346.14(a) (2), (5) through (9), and (b) (1) through (4).*

(A) "Temporarily forms a protective coating over inflamed tissues to help prevent drying of tissues."

(B) "Temporarily protects irritated areas."

(C) "Temporarily relieves burning."

(D) "Provides temporary relief from skin irritations."

(E) "Temporarily provides a coating for relief of anorectal discomforts."

(F) "Temporarily protects the inflamed, irritated anorectal surface" (select one of the following: "to help make bowel movements less painful" or "from irritation and abrasion during bowel movement").

(G) "Temporarily protects inflamed perianal skin."

(H) "Temporarily relieves the symptoms of perianal skin irritation."

(iv) *For products containing aluminum hydroxide gel identified in § 346.14(a)(1) and for products containing kaolin identified in § 346.14(a)(4).* "For the temporary relief of itching associated with moist anorectal conditions."

(v) *For products for external use only containing any analgesic, anesthetic, and antipruritic identified in § 346.16.*

(A) "For the temporary relief of" (select one or both of the following: "pain" or "burning").

(B) "Can help distract from pain."

(C) "May provide a cooling sensation."

(vi) *For products for external use only containing hamamelis water identified in § 346.18(b), and for products for external use and/or intrarectal use containing calamine or zinc oxide identified in 346.18 (a) and (c).*

(A) "Aids in protecting irritated anorectal areas."

(B) "Temporary relief of" (select one or both of the following' "irritation" or "burning").

(vii) *For products for external use only containing any ingredient identified in § 346.20.* The indication in paragraph (b)(1) of this section applies.

(c) *Warnings.* Warnings applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting warning is clear and understandable. The labeling of the product contains the following warnings under the heading "Warnings":

(1) "If condition worsens or does not improve within 7 days, consult a doctor."

(2) "Do not exceed the recommended daily dosage unless directed by a doctor."

(3) "In case of bleeding, consult a doctor promptly."

(4) *For products for external use only.* "Do not put this product into the rectum by using fingers or any mechanical device or applicator."

(5) *For products for intrarectal use to be used with a special applicator such as a pile pipe or other mechanical device.* "Do not use this product with an applicator if the introduction of the applicator into the rectum causes additional pain. Consult a doctor promptly."

(6) *For products for external use only containing any local anesthetic identified in 346.10, menthol identified in § 346.16(c), or resorcinol identified in § 346.20(b).* "Certain persons can develop allergic reactions to ingredients in this product. If the symptom being treated does not subside or if redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a doctor."

(7) *For products containing any vasoconstrictor identified in § 346.12.*

(i) "Do not use this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland unless directed by a doctor."

(ii) *"Drug interaction precaution.* Do not use this product if you are presently taking a prescription drug for high blood pressure or depression, without first consulting your doctor."

(iii) For products containing ephedrine sulfate identified in § 346.12(a). "Some users of this product may experience nervousness, tremor, sleeplessness, nausea, and loss of appetite. If these symptoms persist or become worse, consult your doctor."

(8) *For products containing aluminum hydroxide gel identified in § 346.14(a)(1) and for products containing kaolin identified in § 346.14(a)(4).* "Remove petrolatum or greasy ointment before using this product because they interfere with the ability of this product to adhere properly to the skin area."

(9) *For products for external use only containing resorcinol identified in § 346.20(b).* "Do not use on open wounds near the anus."

(d) *Directions.* Directions applicable to each active ingredient of the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable. The labeling of the product contains the following information under the heading "Directions":

(1) *"Adults:* When practical, cleanse the affected area" (select one or both of the following: "with mild soap and warm water and rinse thoroughly" or "by patting or blotting with an appropriate cleansing pad"). "Gently dry by patting or blotting with toilet tissue or a soft cloth before application of this product." [Other appropriate directions in this section may be inserted here.] "Children under 12 years of age: consult a doctor."

(2) *For products for external use only.* "Apply externally to the affected area" (insert appropriate time interval of administration as identified in paragraphs (d)(6), (7), (8), or (9) of this section).

(3) *For products for external use that are pads containing anorectal ingredients.* "Gently apply to the affected area by patting and then discard."

(4) *For products for intrarectal use that are wrapped suppositories.* "Remove wrapper before inserting into the rectum."

(5) *For products for intrarectal use that are to be used with a special applicator such as a pile pipe or other mechanical device.* "FOR INTRARECTAL USE: Attach applicator to tube. Lubricate applicator well, then gently insert applicator into the rectum."

(6) *For products for external use only containing any of the local anesthetics identified in § 346.10; analgesics, anesthetics, and antipruritics identified in § 346.16; or alcloxa or resorcinol identified in § 346.20.* Apply to the affected area up to 6 times daily.

(i) *For products for external use only containing dibucaine or dibucaine hydrochloride identified in § 346.10 (c) and (d).* Apply to the affected area up to 3 or 4 times daily.

(ii) *For products for external use only containing pramoxine hydrochloride identified in § 346.10(g).* Apply to the affected area up to 5 times daily.

(7) *For products containing vasoconstrictors identified in § 346.12.* Apply to the affected area up to 4 times daily.

(8) *For products for external use only containing glycerin identified in § 346.14(a)(3) or hamamelis water identified in § 346.18(b), and for products for external and/or intrarectal use containing any protectant identified in § 346.14(a) (1), (2), (4), (5), (6), and (8), and (b) (1), (2), (3), and (4), or any astringent identified in § 346.18 (a) and (c).* Apply to the affected area up to 6 times daily or after each bowel movement.

(9) *For products containing petrolatum or white petrolatum identified in § 346.14(a) (7) and (9).* Apply liberally to the affected area as often as necessary.

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 346.52 Labeling of permitted combinations of anorectal active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of this part. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of this subpart.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of this subpart.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of this subpart.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of this subpart. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not exceed any maximum dosage limits established for the individual ingredients in the applicable OTC drug monograph.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

4. The authority citation for 21 CFR Part 369 continues to read as follows:

Authority: Secs. 502, 503, 506, 507, 701, 52 Stat. 1050–1052 as amended, 1055–1056 as amended, 55 Stat. 851, 59 Stat. 463 as amended (21 U.S.C. 352, 353, 356, 357, 371); 21 CFR 5.10 and 5.11.

§ 369.20 [Amended]

5. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the statement, "See also Rectal Preparations for additional warnings," from the entry for "BELLADONNA PREPARATIONS AND PREPARATIONS OF ITS ALKALOIDS (ATROPINE, HYOSCYAMINE, AND SCOPOLAMINE (HYOSCINE)); HYOSCYAMUS, STRAMONIUM, THEIR DERIVATIVES, AND RELATED DRUG PREPARATIONS."

§ 369.20 [Amended]

6. In Subpart B, § 369.20 *Drugs; recommended warning and caution statements* is amended by removing the entry "RECTAL PREPARATIONS FOR EXTERNAL USE."

Dated: May 2, 1988

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 88–18200 Filed 8–12–88; 8:45 am]

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