federal register

Tuesday
May 27, 1980

Part II

Department of Health and Human Services

Food and Drug Administration

Anorectal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 346

[Docket No. 80N-0050]

Anorectal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule 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. The proposed rule, based on the recommendations of the Advisory Review Panel on OTC Hemorrhoidal Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by August 25, 1980 and reply comments by September 24, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on January 24, 1978, a report of the Advisory Review Panel on OTC Hemorrhoidal Drug Products. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC anorectal drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditons excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of the FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. After reviewing all comments submitted in response to this proposal, FDA will issue a tentative final regulation in the **Federal Register** to establish a monograph for OTC anorectal drug products.

The agency recognizes that extensive changes will result in the marketing practices of anorectal drug products if the Panel's recommendations are fully implemented. For example, the Panel found that few clinical studies have been conducted in the anorectal area and recommended that studies be conducted in this area to reclassify Category III conditions to Category I. The Panel has also proposed final formulation testing for anorectal combination products.

The agency notes that the Panel's decision to place pramoxine hydrochloride in Category I was based primarily on data submitted by one manufacturer. Because the Panel based its conclusions on these data, and because it was concerned about the bioavailablity of final formulations of anorectal preparations, the Panel concluded that only pramoxine hydrochloride in these specific formulations can be generally recognized as safe and effective for OTC external use in anorectal drug products. The Panel's Category I recommendation was conditioned upon the disclosure of the exact formulation of each pramoxine hydrochloride-containing product. Subsequently, after adoption of the Panel's report, FDA contacted the manufacturer for permission to include the exact formulation in the proposed monograph. The manufacturer agreed by letter to permit the formulations to be disclosed in the monographs, but did not agree to disclosing the quantities of each ingredient. This letter has been included in OTC volume 120084. (See part I. paragraph D. below—Referenced OTC Volumes.) Accordingly, the monograph specifies only the quantity of pramoxine hydrochloride but not the quantities of the other ingredients in the formulations. The agency recognizes that the Panel's recommendation for pramoxine hydrochloride is unusual in that it has placed only two specific formulations in Category I. The agency invites comment on this approach and whether these formulations or any other formulation for pramoxine hydrochloride should be included in the final monograph.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), the Panel and FDA have held as confidential all information concerning OTC anorectal drug products submitted for consideration by the Advisory Review Panel. All the submitted information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after June 19, 1980, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and are not misbranded (Category I), be effective 30 days after the date of publication of the final monograph in the **Federal Register**.

2. That the conditions excluded from the monograph because they would cause the drug to be not generally recognized as safe and effective or to be misbranded (Category II), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register**, regardless of whether further testing is undertaken to justify their future use.

3. That the status of Category III conditions after publication of a final order is the subject of the recent court decision in the case of *Cutler* v. *Kennedy*, 475 F Supp. 838 (D.D.C. 1979). In that case, the court held that "FDA may not lawfully maintain Category III in any form in which drugs with Category III conditions* * * are exempted from enforcement action" (*Cutler, supra* at 856). The Court issued an order that declared the OTC drug regulations (21 CFR 330.10) unlawful to the extent that they authorize the

marketing of Category III drugs after a final monograph, and enjoined the FDA from implementing any portion of the regulations that authorizes such marketing. In the **Federal Register** of May 13, 1980 (45 FR 31422), FDA issued a proposal to revise the procedural regulations governing the review and classification of OTC drug products to delete the provision that authorizes the marketing of a Category III condition in an OTC drug product after a final monograph. The term Category III, however, may continue to be used prior to publication of a final monograph.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC anorectal drug products was issued in the **Federal Register** of April 26, 1973 (38 FR 10307).

The Commissioner appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety, effectiveness, and labeling of those products: Claude Emerson Welch, M.D., Chairman, Leon Banov, Jr., M.D., Eugene A. Castiglia, M.D., Winston H. Gaskin, R.Ph., Jean Dace Golden, M.D., Thaddeus S. Grosicki, Ph.D., Judith Karen Jones, M.D., Ph.D.

The Panel was first convened on July 9, 1973 in an organizational meeting. Working meetings were held on September 6 and 7, October 7 and 8, December 8 and 9, 1973; February 3 and 4, March 9 and 10, May 12 and 13, August 3 and 4, September 21 and 22, November 1 and 2, December 13 and 14, 1974; January 31 and February 1, March 9 and 10, May 1, 2, and 3, June 30 and July 1, September 8 and 9, November 16 and 17, 1975; January 3 and 4, March 14 and 15, May 1 and 2, July 9 and 10, August 20 and 21, November 21, 22 and 23, December 20 and 21, 1976; January 22 and 23, February 20 and 21, April 29 and 30, August 25, 26, and 27, 1977; and January 22, 23, and 24, 1978. The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA–305), Food and Drug Administration (address above).

Two nonvoting liaison representatives served on the Panel. Allen J. Seeber, nominated by the Consumer Federation of America, served as the consumer liaison and Garrett Swenson, R.Ph., Esq., nominated by the Proprietary Association, served as the industry liaison until he resigned from the Panel in October 1974, and was followed by Hugh Miller, M.D., who was also nominated by the Proprietary Association. The following FDA employees also served: Samuel Jacques Sunnenblick, M.D., served as Executive Secretary until February 1974, and was followed by Clyde G. Oberlander, R.Ph.; Thomas DeCillis, R.Ph., served as Panel Administrator; Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1973, and was followed by Lloyd Scott, R.Ph., who served until April 1974, and was followed by Gary P. Trosclair, R.Ph.

In addition to the Panel members and liaison representatives, the following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request: John Adriani, M.D., M. F. Bartlett, Ph.D., John Behrman, M.D., Robert G. Blank, Ph.D., Eric G. Comstock, M.D., I. Kelman Cohen, M.D., W. R. Darrow, M.D., R. M. Diener, D.V.M., Frank Engley, Ph.D., Arthur D. Flanagan, M.D., Jock L. Graeme, M.D., Richard A. Hopping, M.D., Thomas K. Hunt, M.D., Joseph L. Kanig, Ph.D., Ben Marr Lanman, M.D., Louis Lasagna, M.D., Myron Lover, Ph.D., James D. MacLowery, M.D., Howard I. Maibach, M.D., Juha Niinikoski, M.D., Ronald Okun, M.D., Alan Parks, M.D., Hans J. Rosenbach, R.Ph., Jay P. Sanford, M.D., T. Werner Schwarz, Ph.D., Garrett W. Swenson, Esq., Mark E. Thoman, M.D., Donald D. Trunkey, M.D., Jouni Uitto, M.D., Ph.D., Le Roy Van Dam, M.D., Alexander G. Vongries, M.D., James C. White, M.D., Bengt Zederfeldt, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through January 24, 1978, in arriving at its conclusions and recommendations.

The charge to the Panel required the review of OTC hemorrhoidal ingredients. However, the Panel concluded early in its deliberations that the term "hemorrhoidal" was too restrictive because it narrowed the review to relief of symptoms due to only one type of anorectal disorder. Therefore, the Panel interpreted the charge to encompass not only relief of symptoms due to hemorrhoidal disease, but also relief of symptoms of disease in the perianal, anal canal, and/or the lower rectal area. The Panel recommends that the ingredients

reviewed in this document be referred to as "anorectal" ingredients as a more accurate designation of the area in which symptoms are being relieved. (See part I. paragraph C. below—Classification of Ingredients and part II. paragraph A.1. below—Introduction.)

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC anorectal drug products are set out in three categories:

Category I. Conditions under which OTC anorectal drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC anorectal drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

I. Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of April 26, 1973 (38 FR 10307) requesting the submission of data and information on hemorrhoidal drugs, the following firms made submissions relating to the indicated products:

A. Submissions by Firms

Firm	Marketed products
Abbott Laboratories, North Chicago, IL 60064	Tronothane Hydrochloride 1% Topical Local Anesthetic Cream, Tronothane Hydrochloride 1% Topical Local Anesthetic Jelly.
Astra Pharmaceutical Products, Inc., Worcester, MA 01606	Xylocaine Topical Anesthetic Ointment 2.5%.
Astro-Solar Laboratories, Wheatfield, IN 46392	Tengum.
Bellwood Pharmaceutical Co., Philadelphia, PA 19151	Hemozone.
Bristol-Myers Co., New York, NY 10022	Pazo Hemorrhoid Ointment, Pazo Hemorrhoid Suppositories, Aerosol Medicated Anal Wipe Foam.
Chesebrough-Pond's, Inc., Trumbull, CT 06611	Vaseline Pure Petroleum Jelly.
Ciba-Geigy Corp., Summit, NJ 07901	Nupercainal Anesthetic Ointment, Nupercainal Suppositories.
Combe, Inc., White Plains, NY 10601	Lanacane Creme.
Dr. Kade Pharmazeutische, Fabrik GmbH, Berlin, Germany	Posterisan Suppositories, Posterisan Ointment, Posterisan Combi-Package.
Fuller Laboratories, Inc., Eden Prairie, MN 55343	Tucks Cream, Tucks Medicated Pads, Tucks Ointment, Tucks Take-Alongs.
Merrell-National Laboratories, Cincinnati, OH 45215	Diothane Ointment.
Phenex Laboratories, Chicago, IL 60641	Phenex Rectal Suppositories.
Philips Roxane Labs., Inc., Columbus, OH 43216	Gentz Wipes.
Pitman-Moore, Indianapolis, IN 46268	Dyclonine Hydrochloride.
Quist Chemical Co., Niagara Falls, NY 14304	Quist Ointment.
Reed & Carnrick Pharmaceuticals, Kenilworth, N.J. 07033	Non-Steroid Proctofoam.
Resinol Chemical Co., Baltimore, MD 21201	Resinol Greaseless Cream, Resinol Ointment.
The Upjohn Co., Kalamazoo, MI 49001	Epinephricaine Rectal Ointment, Tanicaine Rectal Ointment, Tanicaine Rectal Suppositories.
Warner-Chilcott Laboratories, Morris Plains, NJ 07950	Anusol Hemorrhoidal Suppositories, Anusol Ointment.
Whitehall Laboratories, Inc., New York, NY 10017	Preparation H Hemorrhoidal Ointment, Preparation H Hemorrhoidal Suppositories.
Winthrop Laboratories, New York, NY 10016	PNS Rectal Suppositories, Pontocaine Cream, Pontocaine Ointment.
Wyeth Laboratories, Inc., Philadelphia, PA 19101	Protogel, Wyanoid Hemorrhoidal Ointment, Wyanoids Hemorrhoidal Suppositories.

In addition, the following firms or individuals made related submissions:

Firm	Marketed products
American Home Products Corp., New York, NY 10017	Supplemental Submissions on Skin Respiratory Factor (SRF).
Angle, Carol R., M.D., University of Nebraska Medical Center, Omaha, NE 68105.	Toxicity of Camphor.
Arnar-Stone Laboratories, Inc., Mount Prospect, IL 60056	Benzocaine.
Astra Pharmaceutical Products, Inc., Worcester, MA 01606	Supplement to Xylocaine Ointment.
Bristol-Myers Co., New York, NY 10022	Remarks on Combination Policy.
Chesebrough-Pond's Inc., Trumbull, CN 06611	Clinical Studies on Vaseline Petroleum Jelly.
Ciba-Geigy Corp., Summit, NJ 07901	Dibucaine, Acetone Sodium Bisulfite, Presence of Sensory Receptors Within Rectal Mucosa.
Combe, Inc., White Plains, NY 10604	Resorcinol, Irritation Studies on Lanocaine.
Dow Chemical Co., Indianapolis, IN 46268	Supplemental Submission on Dyclone Creme 1%.
Fuller Laboratories, Inc., Eden Prairie, MN 55343	Hamamelis Water.
Humphreys Pharmacal, Inc., Rutherford, NJ 07070	Hamamelis Water.
Merrell-National Laboratories, Cincinnati, OH 45215	Oxyquinoline Benzoate and Diperodon.
Meyer Laboratories, Inc., Fort Lauderdale, FL 33316	Protocol for a Study Comparing Corticaine Cream with Appropriate Controls in the Relief of Symptoms and Inflammation Associated with Acute Hemorrhoids.
Pfizer Pharmaceuticals, New York, NY 10017	Benzyl Alcohol.
Phenex Antiseptic Laboratories, Inc., Chicago, IL 60614	In Vivo and In Vitro Studies of Sodium Salicylic Acid as a Bacterial and Fungal Antiseptic.
The Proprietary Association, Washington, DC 20006	Statement Concerning the Criteria for Placing Category III Ingredients into Category I, Statement on Principles Applicable to Combination Products, Statement on Final Product Testing, Comment on Testing Guidelines.
Schuylkill Chemical Co., Philadelphia, PA 19132	Additional Information on Alcloxa and Allantoin.
Sterling Drug, Inc., New York, NY 10016	Phenylephrine Hydrochloride, Tyloxapol, Tetracaine Hydrochloride.
Trunkey, M.D., San Francisco, CA 94122	Donor Site Wound Protocol.
Whitehall Laboratories, New York, NY 10017	Live Yeast Cell Derivative, The Safety and Effectiveness of SRF as a Wound Healing Agent, Comment on Labeling Claim of "Temporarily Shrinks".

B. Labeled Ingredients Contained in Marketed Products Submitted to the Panel

Acetone sodium bisulfite, alcloxa, amaranth, aromatic oils, atropine, beeswax, benzalkonium chloride, benzocaine, benzyl alcohol, benzyl benzoate, bismuth oxyiodide, bismuth resorcin compound [1], bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, boric acid, boric acid glycerite, cocao butter, calamine, camphor, carbowaxes, cetylpyridinium chloride, chlorobutanol, chlorothymol, cocoa butter, dibucaine, diperodon, dyclonine hydrochloride, *E. coli* vaccines, ephedrine sulfate, epinephrine, eucalyptus oil, extract belladonna, extract of collinsonia (stone root), extract of lappa (burdock root), extract of leptandra (culver's root), gel of alumina, glycerine, goldenseal, hamamelis water (witch hazel water), kaolin, lanolin, lidocaine base, live yeast cell derivative, menthol, methylparaben, mineral oil, mullein, myrrh, oil of cade, oil of mace, oil of turpentine, peruvian balsam, petrolatum, petroleum base, phenacaine hydrochloride, phenol, phenylephrine hydrochloride, phenylmercuric nitrate, paramoxine hydrochloride, prepared calamine, propylene glycol, resorcin, resorcinol, secondary-amyltricresols, shark liver oil, skin respiratory factor, sodium bisulfite, sodium salicylic acid phenolate [2], sulphur, tannic acid, tetracaine, tetracaine hydrochloride, tyloxapol, white wax, white petrolatum, zinc oxide.

[1] This ingredient appears on the label of a product submitted for review; however, it is not an identifiable chemical compound, nor is it officially recognized in the standard compendia. It is a mixture of 50 percent bismuth oxide and 50 percent resorcinol. For the purposes of this report, discussions will be written on bismuth oxide and resorcinol.

[2] This ingredient appears on the label of a product submitted for review; however, it is not an identifiable chemical compound, nor is it officially recognized in the standard compendia. For the purposes of this report, discussion will be focused under sodium salicylic acid phenolate.

Ingredients reviewed by the Panel in addition to the labeled ingredients contained in marketed products submitted to the Panel: Bismuth oxide, coconut oil (palm kernel oil), cod liver oil, dibucaine hydrochloride, epinephrine hydrochloride, epinephrine undecylenate, polyethylene glycol ointment, starch, vitamin A, vitamin D, wool alcohols.

C. Classification of Ingredients

1. *Anorectal active ingredients.* The Panel considered the ingredients with regard to their effect on symptoms related to the perianal, anal, and/or lower rectal areas. As discussed elsewhere in this document, the Panel chose the designation "anorectal ingredients" as more accurately describing the use of these ingredients rather than "hemorrhoidal ingredients." The Panel, therefore, will use the term "anorectal" in referring to these ingredients. (See part II. paragraph A.1. below— Introduction.)

The Panel has classified the following anorectal ingredients submitted to the Panel into groups identified below:

Local Anesthetics

Benzocaine in polyethylene glycol ointment (benzocaine), benzyl alcohol, dibucaine, dibucaine hydrochloride, diperodon, dyclonine hydrochloride, lidocaine (lidocaine base), phenacaine hydrochloride, pramoxine hydrochloride in a cream formulation (pramoxine hydrochloride), pramoxine hydrochloride in a jelly formulation (pramoxine hydrochloride), tetracaine, tetracaine hydrochloride.

Vasoconstrictors

Ephedrine sulfate in aqueous solution (ephedrine sulfate), epinephrine, epinephrine hydrochloride in aqueous solution (epinephrine hydrochloride), epinephrine undecylenate, phenylephrine hydrochloride in aqueous solution (phenylephrine hydrochloride suppositories (phenylephrine hydrochloride).

Protectants

Aluminum hydroxide gel (gel of alumina), bismuth oxide, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, calamine (prepared calamine), cocoa butter (cacao butter), cod liver oil, glycerin in aqueous solution (glycerine), kaolin, lanolin, mineral oil, shark liver oil, starch, white petrolatum (petrolatum, petroleum base), wool alcohols, zinc oxide.

Counterirritants

Camphor, hydrastis (golden seal), juniper tar (oil of cade), menthol, menthol in aqueous solution, turpentine oil, rectified (oil of turpentine).

Astringents

Calamine (prepared calamine), tannic acid, witch hazel water (hamamelis water), zinc oxide.

Wound-Healing Agents

Cod liver oil, live yeast cell derivative (skin respiratory factor), peruvian balsam, shark liver oil, vitamin A, vitamin D preparations (ergocalciferol and cholecolciferol).

Antiseptics

Boric acid, boroglycerin (boric acid glycerite), hydrastis (golden seal), phenol, resorcinol (resorcin), sodium salicyclic acid phenolate.

Keratolytics

Alcloxa, resorcinol (resorcin), precipitated sulfur (sulphur), sublimed sulfur (sulfur).

Anticholinergics

Atropine, belladonna extract (extract belladonna).

2. Miscellaneous labeled anorectal active ingredients

Collinsonia extract (extract of collinsonia, stone root), *E. coli* vaccines, lappa extract (extract of lappa, burdock root), leptandra extract (extract of leptandra, culver's root), mullein.

3. Ingredients submitted to the Panel and classified as inactive and/or pharmaceutical necessity ingredients

Acetone sodium bisulfite, amaranth, aromatic oils, beeswax, benzolkonium chloride, benzyl benzoate, bismuth oxyiodide, carbowaxes, cetylpyridinium chloride, chlorobutanol, chlorothymol, coconut oil (palm kernel oil), eucalyptus oil, mace oil (oil of mace), methylparaben, myrrh, phenylmercuric nitrate, polyethylene glycol ointment, propylene glycol, secondary amyltricresols (secondary-amyltricresols), sodium bisulfite, tyloxapol, white wax.

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call for data notice published in the **Federal Register** of April 26, 1973, (38 FR 10307). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 26, 1980, in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. General Comment

1. *Introduction.* The Advisory Review Panel on OTC Hemorrhoidal Products was charged with the review and evaluation of the safety and effectiveness of single ingredients as well as combinations of such ingredients when used in OTC products for the relief of symptoms associated with hemorrhoids. The Panel interpreted that request as a charge to evaluate products used for the relief of symptoms of disease in the perianal, anal canal, and/or the lower rectal areas. The Panel concludes that when a consumer complains of "piles, hemorrhoids, or rectal problems," the implication is a difficulty in the perianal area, anal canal, and/or the lower rectum.

The Panel finds the term "hemorrhoidal" too restrictive when OTC preparations for "hemorrhoidal disease" are considered. Therefore, instead of the term "hemorrhoidal disease," the terms "anorectal disorders" and/or "anorectal disease" were chosen by the Panel as a more accurate designation, which is defined as those conditions in the lower part of the intestinal tract that interfere with its normal function and/or sensation. The Panel recommends to industry, the medical community, and consumers the use of the term "anorectal" so that in the future a uniform concept is communicated by all.

Anorectal disorders are characterized by the symptoms and signs of bleeding, pain, burning, itching, discomfort, seepage, swelling, protrusion, irritation, inflammation, and changes in bowel pattern or any combination thereof, and may be due to various causes that will be discussed later in this document. (See part II. paragraph E. Below—Therapeutic Claims and Their Rationale.) Not all of these symptoms and signs are amenable to self-diagnosis or self-treatment.

The Panel is aware that there has been no concerted effort to study anorectal disorders and, consequently, our generation has inherited the age-old and difficult problem of treating anorectal diseases empirically. Banov (Ref. 1) has stated that the U.S. Government has spent over 50 billion dollars to study the backside of the moon but not one red cent to study the backsides of its citizens. Unless a concerted effort is undertaken to stimulate research in the anorectal area, the problem will just be passed to the next generation. The Panel on OTC Hemorrhoidal Products is pleased to serve in the review process, knowing that this Panel's work represents the first expenditure of Federal funds related to the study of anorectal disorders.

Anorectal disease, though rare in other animals, is extremely common in humans. No human is immune. The vast majority of adults suffer from one or more anorectal symptoms at some time in their life (Ref. 2). Anorectal disease has caused an unaccountable number of man-hours to be lost annually in industry, commerce, agriculture, and in the military. As with the common cold, millions of Americans have suffered or will suffer from anorectal diseases because of the absence of study programs to increase the knowledge of how to prevent and to treat the diseases of the anorectum (Ref. 2).

Factors thought to contribute to the current high incidence of these disorders are the upright position of man, an increased use of refined foods (lack of roughage), increased sedentary life (lack of physical activity), decreased daily liquid intake, and present day "over concern" with bowel function, leading to the indiscriminate use of laxatives and enemas as indicated in the findings of the Advisory Review Panel on OTC Laxatives, Antidiarrheal, Emetic and Antiemetic Drug Products published in the **Federal Register** of March 21, 1975 (40 FR 12902).

The first task for the Panel was to accumulate and verify available information, identify misinformation, and establish basic definitions and concepts. Next, a review of the history of anorectal diseases and the assessment of the status of present-day knowledge, of lay and professional people alike, concerning these conditions was developed. In searching for the earliest records, one turns to the medical writings of ancient Egypt where specialists, who treated anorectal diseases, amassed a remarkable amount of practical knowledge. The Egyptians employed suppositories frequently in a variety of anorectal disorders (Ref. 3). They used fatty and oleaginous compounds which this Panel calls emollients.

The Chester Beatty Medical Papyrus, the earliest known treatise, completely devoted to anorectal diseases, presents practical remedies to treat anorectal and other disorders, even though treatment was based entirely on symptoms rather than on specific diseases (Ref. 3).

In 1835, in London, St. Mark's Hospital for Fistula and Other Diseases of the Rectum was founded. This hospital continues to be the mecca where those interested in rectal and colonic diseases come to study. One American, Dr. Charles Boyd Kelsey, was so impressed with St. Mark's Hospital that in 1879, in New York, he started St. Paul's Infirmary (founded on the same general plan as St. Mark's), which has not survived to the present time. Another American, Dr. Joseph Mathews, after studying at St. Mark's, returned to this country and started the American Proctologic Society which later became the present day American Society of Colon and Rectal Surgeons.

In the treatment of anorectal diseases, drugs were employed on an empirical basis. Many of the drugs used throughout history are still in OTC products today. However, modern anorectal therapy emphasizes good anal hygiene as a primary measure and then is followed generally by the application of ingredients which are intended to relieve anorectal symptoms. In many cases, however, treatment may require surgical measures.

Current societal attitudes regarding anorectal diseases encourage secrecy, reticence, shyness, and embarrassment. The average person, as well as some physicians, feels that it is not proper or interesting to talk about anorectal function or diseases. This social and medical shyness regarding the anorectum has contributed to the lack of research relative to diseases of the anorectum.

In early years, child is encouraged to use such euphemisms as "bottom," "fanny," and "behind." Also, the child is taught by the family to use a code name for defecation (bowel movement). The child learns the various terms to avoid saying "toilet" by such evasions as "rest room," "tinkle room," or "potty."

Because ideas relating to the anorectum have not changed significantly over the years by full and open discussion or education, the anorectum has become downgraded and subject to humor. This makes it difficult for consumers with anorectal diseases or conditions to seek out information and/or obtain help for their anorectal problems.

The Panel believes medical schools neglect the teaching of anorectal diseases. This neglect is reflected in the decreased interest of practicing physicians and has produced a relatively high degree of ignorance of anorectal hygiene and diseases which adds to the problem of the affected consumer's desire to obtain relief. There is great confusion and difference of opinion concerning anatomical and physiological terms and definitions. It is not surprising that the consumer does not realize that continued self-treatment of the symptoms associated with "hemorrhoids" may be masking more serious medical problems such as anal fissures, fistulae, abscesses, verrucae acuminatae (anal warts), pruritis ani (anorectal itching), or fecal impactions. The need for direct and early surgical or medical intervention is indicated in treating such diseases as cancer or inflammatory bowel disease. However, it is unusual for serious diseases to respond to treatment with the ingredients in OTC anorectal products within the 7-day limit discussed elsewhere in this document. (See part II. paragraph E. below—Therapeutic Claims and Their Rationale.) This time limit was chosen for protection of the consumer and is intended to alert the consumer to consult a physician for serious problems.

References

(1) Banov, Jr., L., "Backsides," *Archives of Surgery,* 109:844, 1974.

(2) Kramer, B., "Some New Cures Help Hemorrhoid Sufferers Whose Number is Legion. Painful Surgery is Avoided; Among Methods: Freezing; Debunking Some Myths. Napoleon and Paul Fisher," *The Wall Street Journal,* 182:1 and 19, 1973.

(3) Banov, Jr., L., "The Chester Beatty Medical Papyrus: The Earliest Known Treatise Completely Devoted to Anorectal Diseases," *Surgery,* 58:1037–1043, 1965.

2. *Recommendations.* The Panel has made the following recommendations, based on the preceding discussion: a. Promote a study program on the history and management of anorectal diseases to study these diseases on a more scientific basis.

b. Reevaluate, on a scientific basis, drugs that have been discarded but might be of value when examined in light of our increased knowledge, facilities, and techniques.

c. Form a committee with representatives from the American Society of Colon and Rectal Surgeons, and Anatomists Association, the American College of Surgeons, the American Medical Association, and the pharmaceutical industry and profession

to come to grips with the problem of confusion in terminology, and to develop and define terms acceptable to all. This would provide a common working ground from which further studies of anorectal diseases could be instituted.

d. Form research groups to carry out long-range projects on anorectal disease with Federal funding. This implies the development of formalized research methods. For example, there is a need for a camera with fixed focus to be used in anorectal research so that all the pictures would be standardized. With everyone using the same terminology, methods, and the same documentation by photographs, there would be a better chance to advance the knowledge of the management of anorectal diseases. The results could then be given to many groups and would develop a broader basis for discussion, which would lead to a better chance for the meeting of the minds and hopefully lead to improved treatment and possible prevention of anorectal diseases.

e. Establish a greater emphasis on the teaching of diseases of the anorectum and their treatment in medical schools and in resident training programs.

B. Anatomy of the Anorectal Area

The diseases considered in this document are located in the skin of the perianal area, the anal canal, and the lower portion of the rectum. The perianal area is approximately 7 centimeters (cm) in diameter, and surrounds the anus. This area is covered by skin that normally is somewhat more likely to be moist than exposed skin in other areas of the body. The perianal area contains very sensitive pain fibers.

The external opening of the bowel is the anus. Extending upward from the anus is the anal canal which is roughly 2.5 cm in length and also is lined with skin. At the upper margin of the anal canal is the anorectal line which marks the transition of the mucous membrane lining the rectum.

The mucous membrane of the rectum is highly vascular. It contains no indentifiable pain fibers, but there are receptors for the reflex of defecation that are not limited to the rectal mucosa but occur in the muscular wall as well. These sensations allow the differentiation of gas from feces. Such receptors are also present in the anal canal. The nerves, within the muscular wall of the rectum, are known as contraction receptors or pressure receptors; they allow the patient to perceive the pain of distension. Anal continence is maintained by two sphincters. The internal sphincter functions without any conscious control (involuntary), while the external sphincter is a voluntary muscle. The sphincters extend downward beneath the lining of the anal canal. Beneath the mucous membrane in this area is a network of arteries and veins.

There are three main arteries and concomitant viens in this area. They are known as hemorrhoidal arteries and veins and are denoted as internal when they lie above the anorectal line and external when they lie below this line. Blood from these vessels returns either to the general circulation via the inferior and middle hemorrhoidal veins or through the portal system via the superior hemorrhoidal vein.

These vessels that lie just above and below the anorectal line are remarkable in that there is the suggestion of an arteriovenous shunt. Proof of these arteriovenous shunts has been shown by the demonstration of a high oxygen content in these vessels (Ref. 1). To some observers these tissues are similar to the erectile tissues of the corpus cavernosum of the genital tract (Ref. 2).

The following anatomical terms are used within this document and are defined below:

1. *Anal canal.* The anal canal is the channel that connects the end of the gastrointestinal tract (rectum) with the outside of the body. It averages about 2.5 cm in length.

2. *Anal sphincters.* The anal sphincters are those muscles, encircling the anal canal, that provide muscular control and enable an individual to be continent (not spill or leak fecal material). There are two anal sphincters: (1) the external sphincter—a voluntary muscle which functions under the conscious control of the person, and (2) the internal sphincter—an involuntary muscle that functions without the conscious control by the person.

3. *Anal verge (rima).* The anal verge is the lower limit of the anal canal which also represents the junction of the anal canal and the perianal skin.

4. *Anorectal line (dentate line, pectinate line).* The anorectal line marks the division between the upper end of the anal canal and the rectum. It is slightly above the junction of stratified squamous epithelium that lines that anal canal and the columnar epithelium that lines the rectum. It is at the internal side of this line that the anal crypts or glands are found.

5. *Anal crypts.* Anal crypts are pocketlike formations of the mucosa at the anorectal line. Because they face upward, they can retain small amounts of fecal materials which may cause irritation. This irritation is believed by many to be the cause of subsequent infections and the development of some forms of hemorrhoidal disease.

6. *Anus.* The anus is that external opening of the anal canal which connects the rectum with the outside of the body.

7. *External application.* The application of ingredients to the skin of the perianal area and/or the anal canal. This application excludes the use of pile (rectal) pipes, applicators, or suppositories.

8. *Hemorrhoidal blood vessels.* Directly under the mucous membrane is the plexus of hemorrhoidal vessels. There are two types of hemorrhoidal blood vessels: (a) external hemorrhoidal blood vessels—those vessels that are located below the anorectal line, and (b) internal hemorrhoidal blood vessels—those vessels located directly under the mucous membrane of the lowermost part of the rectum, just above the anorectal line.

9. *Hemorrhoidal tissue (anorectal tissue).* The hemorrhoidal tissue is the soft skin, mucosa, fibrous, and fatty tissue that surrounds the hemorrhoidal blood vessels.

10. *Intrarectal (internal) application.* The delivery of anorectal ingredients through the anal canal and into the lower rectum above the anorectal line by some means, such as a rectal pipe or suppository.

11. *Levator ani.* A large group of muscles that form a support for the pelvic organs, including the rectum.

12. *Perianal area.* The perianal area is that portion of the skin and buttocks immediately surrounding the anus.

13. *Rectum.* The rectum is the lower end of the gastrointestinal tract which extends from the anorectal line up to the sigmoid colon. It is approximately 12 to 15 cm in length and is lined with mucous membrane.

References

(1) Thulesius, O. and J. E. Gjores, "Arterio-Venous Anastomoses in the Anal Region with Reference to the Pathogenesis and Treatment of Haemorrhoids." *Acta Chirurgica Scandinavica*, 139:476–478, 1973.

(2) Stelzner, F., "Die Anatomie des Kontinenzorgans," *in* "Die Anorectalen Fisteln," 2d Ed., Springer-Verlag, New York, p. 20, 1976.

C. Anorectal Physiology in a Healthy State

The anus and the anal canal are surrounded by the two circular muscles which together form the anal sphincters. In the normal state, the anal canal and anus are closed, and the individual does not leak fecal material and/or mucus discharge from the rectal mucosa. The muscle can be made to close more tightly under voluntary control.

The anal canal itself is covered with skin and has sensory nerve fibers. This

area shares with the genital organs the characteristic of having increased sensory nerve fibers which, in the presence of disease, can lead to great discomfort. Healthy skin acts as a protective barrier which significantly limits absorption of substances into the body. Therefore, treatment in the area of the anal canal will essentially produce a local effect. In disease, the integrity of the skin barrier is altered and absorption can increase. Loss of protective oils from the cells of the skin itself can lead to damage and/or death of the cells.

The upper end of the anal canal is demarcated by the anorectal line which divides the anal canal from the rectum. The anal crypts are located at this line. They are pockets that in the erect position face upward; they can fill with small amounts of liquid and feces and subsequently are unable to empty themselves. This can lead to irritation and inflammation, which may lead to anorectal disease.

The rectum is lined with a mucous membrane. It does not contain pain sensory nerve fibers. The rectum shares with the rest of the colon only a sense of discomfort when significantly distended. Healthy mucous membrane permits a high degree of absorption of substances, especially water, through the rectal wall. Directly under the mucous membrane is the plexus of hemorrhoidal vessels. There are three divisions of the hemorrhoidal veins by which blood is returned to the heart—the superior, middle, and inferior hemorrhoidal veins. Blood from the superior hemorrhoidal veins drains into the portal system which passes through the liver on the first circulation of blood throughout the body. Blood draining from the inferior and middle hemorrhoidal veins passes into the caval system which by-passes the liver in the first circulation of the blood through the body. Thus, substances which are absorbed through the mucous membrane of the wall of the rectum do not always circulate through the liver to be metabolized. Medication applied into this area may exert a systemic effect due to rectal absorption and immediate transfer into the caval circulation. This can be potentially dangerous with some drugs and will be discussed later in this document. (See part II. paragraph G. below—Bioavailability of Anorectal Dosage Forms and part II. pargraph H. below-Rectal Absorption.)

The anus and anal canal function as an exit through which the body eliminates part of its waste products. It is important to remember that the anorectal area is regularly being covered with feces, which contain digested and undigested food and a multitude of organisms. Healthy skin of the anus and anal canal and healthy rectal mucosa act as a barrier to protect the body from invasion by the bacteria in the feces and from injury due to unabsorbed roughage.

The rectum itself my be empty, except for small amounts of mucous, or may contain feces. When feces are moving down from the colon, they fill and distend the rectum, thereby activating the rectal reflexes which leads to defecation or the passing of the feces out through the anal canal.

The rectal pH varies from nearly netural to highly alkaline (Ref. 1). This pH will influence the absorption or activity of ingredients placed within the rectum. (See part II. paragraph G. 2. c. below—Physiologic factors.)

Reference

(1) Granet, E., "Manual of Proctology," The Yearbook Publishers, Inc., Chicago, IL, pp. 259–260, 1954.

D. The Anorectum in a Diseased State

The anorectal area is subject to a variety of diseases. The most important to the consumer is that of hemorrhoids that are abnormally large or symptomatic conglomerates of blood vessels, supporting tissue, and overlying mucous membrane or skin. When this condition occurs, the consumer will attempt self-treatment first to relieve the symptoms of burning, pain, itching, swelling, and complaints of inflammation or irritation. Other common lesions of the anorectal area include fissures; perianal abscesses; fistulas; warts; and various tumors such as cancer or polyps which can cause persistent symptoms, including bleeding, that are not amenable to self-treatment.

Although many theories are to be found in the literature, the precise causative factor or factors of anorectal disease are not agreed upon. Hence, there are no known means to prevent anorectal disease.

Historically, the chief cause for the development of hemorrhoids has been accepted to be an inadequate venous return and resultant pooling of venous blood. Venous return is made difficult by such considerations as an erect posture and straining during defecation. Because of man's erect position and because there are no valves in the veins of the portal system, there is a network of blood vessels extending from the liver to the anus that will produce continued pressure in the anorectum. A further block of the portal veins by infection or by severe cirrhosis of the liver will increase this pressure and may be followed by the production of hemorrhoids. Pregnancy is associated with increased pelvic pressure and is frequently complicated by hemorrhoids. Heredity may play a role in the tendency to develop anorectal disease.

Another plausible concept to explain the development of anorectal disorders is that, initially, an infection develops in the anal crypts. The infection may exist without the individual even being aware of it. At some unpredictable time the inflammation spreads. It veins are near the inflamed crypt, an inflammation about the veins (periphlebitis) may develop which would involve the vein wall (phlebitis), then the vein lining (endophlebitis), and end up with clot formation (thrombophlebitis), which is known clinically as a thrombosed hemorrhoid. Sometimes the vein wall ruptures and blood infiltrates the tissues outside the vein, producing a hematoma. This is also known as a thrombosed hemorrhoid. Also, the inflammation of the crypt may be the cause of a fissure, abscess, or fistula.

Increased inflammation followed by pain that causes the individual to become aware of the anorectal region. The greater the inflammation, the greater the pain. Sometimes the anorectal inflammation may subside spontaneously. Some OTC anorectoal products claim to contribute to reduction of inflammation. On the other hand, the inflammation may progress and require treatment by a physician.

Stelzner (Ref. 1) has advanced the novel and plausible concept that hemorrhoids resemble the corpus cavarnosum penis. He observed the resemblance of the connective tissue architecture of hemorrhoids with that of corpus cavernosum penis and further noted that the large vascular cavities were filled directly by arteries or arteriovenous anastomoses. The blood in the vessels was present only as a filling material. There were no capillaries present in the corpus. Morevoer, the bleeding in and around the anal canal was predominately arterial. The corpus cavernosum has been demonstrated by arteriography. This concept is consistent with the findings of Thulesius and Gjores (Ref. 2) who showed by gas analysis that the blood in the hemorrhoids was arterial blood. This new concept may provide insight into other possible methods of treatment.

References

(1) Stelzner, F., "Die Anatomie des Kontinenzorgans," *in* "Die Anorectalen Fisteln, 2d Ed., Springer-Verlag, New York, p. 20, 1976.

(2) Thulesius, O. and J. E. Gjores, "Arterio-Venous Anastomoses in the Anal Region with Reference to the Pathogenesis and Treatment of Haemorrhoids," *Acta Chirurgica Scandinavica*, 139:476–478, 1973.

The Panel has developed the following definitions for important diseases affecting the anorectal area:

1. *Hemorrhoids.* Hemorrhoids are abnormally large or symptomatic conglomerates of blood vessels, supporting tissues, and overlying mucous membrane or skin of the anorectal area.

2. *Internal hemorrhoid.* An abnormal conglomerate mass of blood vessels and swollen tissues that arises above the anorectal line.

3. *External hemorrhoid.* An abnormal conglomerate mass of blood vessels and swollen tissues that arises below the anorectal line. The designation "hemorrhoids" is used interchangeably with "piles" and is understood by the consumer to be a swelling. It constitutes a very large part of anorectal conditions for which the consumer seeks relief. Adults between 20 and 50 years of age show the highest rate of incidence and most frequently have more than one anorectal symptom.

4. *Skin tags.* Remnants of hemorrhoids which have recovered from swelling but did not fully return to their original condition.

5. *Thrombosed external hemorrhoid.* A clot that develops in a hemorrhoidal vein in the anal or adjacent to the anus, or a rupture of a hemorrhoidal vessel and an accumulation of blood beneath the skin.

6. *Prolapsed hemorrhoid.* A protrusion of enlarged internal hemorrhoids into the anal canal or extending through the anus.

7. *Rectal prolapse.* A protrusion of a portion of the rectal wall through the anal canal. It may or may not involve the whole circumference of the rectal tissue but usually includes hemorrhoids. It is a serious condition requiring the attention of a physician.

8. *Perianal, perianorectal, or perirectal abscess (collection of pus).* An infection caused by the penetration of bacteria into subcutaneous or submucosal tissues resulting in a localized collection of pus.

9. *Anal fistula (fistula-in-ano).* An inflamed channel or tract connecting the anorectum and the perianal skin which develops due to increased pressure from bacterial infection in the submucosal and subcutaneous anorectal tissues, and which may discharge feces and/or pus intermittently.

10. *Anal fissure (fissure-in-ano).* A painful crack or ulcer in the skin of the anal canal.

11. *Pruritus ani (anal itch).* The medical term denoting persistent itch in the perianal area and/or anal canal.

12. *Anorectal cancer.* A malignant tumor usually manifested by bleeding, change in bowel habit, and/or a constant desire to defecate unrelieved by the passage of a stool.

13. *Polyp.* A benign tumor consisting of mucous membrane and submucosal tissues arising in the rectum.

E. Therapeutic Claims and Their Rationale

The Panel emphasizes that the main objective in the treatment of anorectal disease by OTC preparations is the relief of symptoms associated with anorectal disorders and disease. Consequently, it is necessary to identify the important symptoms that occur with anorectal disease and then to discuss the pharmacologic groups of agents that are intended to relieve these specific symptoms. This is summarized in a chart elsewhere within this document. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.)

Any discomfort of the anorectal area is, at the outset, usually regarded as resulting from irritation of inflammation. Most people tend to consider symptoms of bleeding, pain, itching, burning, seepage, swelling, or protrusion to be caused by or associated with hemorrhoids and buy "hemorrhoidal" preparations to relieve these symptoms. However, these symptoms can be caused by a variety of disease conditions. (See part II. paragraph D. above—The Anorectum in a Diseased State.) Accordingly, the Panel emphasizes that OTC anorectal preparations can relieve certain symptoms but do not necessarily cure diseases. Symptoms should be significantly relieved, if not completely cleared, in reasonable period of time, i.e., in 7 days, and the Panel, therefore, concludes that if symptoms persist for more than 7 days, the consumer should consult a physician.

1. *Itching.* It is produced by a mild stimulus of the sensory nerve fibers which leads to scatching. This symptom is also called pruritus and occurs with many anorectal disorders. When itching persists in the anal and perianal area, despite good hygiene and the use of the usual anorectal products, it is termed pruritus ani. The Panel is aware that the most common symptom of all anorectal disorders is "itching" and that all anorectal active ingredients directly or indirectly deal with this symptom to some degree. The words "itching" and "anal itching" are assumed, in the rest of this document, to refer to the anal and/or the perianal areas.

Itching has affected mankind throughout the ages. Ancient Egyptian medical records list many remedies to treat anal itching; some of them are still employed today.

The causes of anal itching can be classified into several different groups. In general, itching can be secondary to swelling on moisture in this area. It may be due to local sensitivity of the skin to irritants in clothes, in detergents, or in fecal contents. Fungal infections that may be associated with diabetes mellitus or parasites, e.g., anorectal pathologic lesions and pinworms, can also cause itching. In some instances, the precise cause cannot be determined and in others it appears to be due to some psychological cause. However, the individual with intense anal itch is more concerned about relief than the cause.

The Panel has defined antipruritic agent as one that relieves itching and has concluded that local anesthetics, vasoconstrictors, protectants, counterirritants, astringents, wound-healing agents, antiseptic, and keratolytics act as antipruritics. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.) Products containing any Category I ingredient in these groups will be allowed to claim "relief of itching" as designated within the appropriate Category I labeling section within this document.

An important factor that most often leads to symptomatic relief of itching from anorectal disorders is improved anal hygiene. In connection with good health practices involving the lower part of the torso, vaginal hygiene has been stressed, but little has been said about anal hygiene. Washing the anorectal area with soap with water and carefully removing the soap on a daily basis and after each bowel movement greatly aids in the relief of symptoms and may prevent recurrence of perianal itching. Of importance in anal hygiene is patting or blotting rather than rubbing the skin of the irritated perianal area to avoid further irritation. Patients with anorectal symptoms should be encouraged to sit in warm water as an additional simple means of therapy, two to three times daily, for 15 to 29 minutes; this is called a sitz bath.

The labeling of anorectal products must state that if itching persists for more than 7 days, consult a physician because it is much easier to relieve the symptoms of an acute case of itching than it is to treat a chronic case. (See part II. paragrpah Q. below—Labeling.)

2. *Burning.* Burning is considered, in relationship to itching, to be the next

higher degree or irritation of sensory nerves in the anorectal area. Such sensations vary from a mild itch to be a sensation of pain described as intense heat, such as occurs after picking up hot objects without protection. The relief of burning can be obtained by use of some anorectal ingredients such as local anesthetics, protectants, counterirritants, astringents, wound-healing agents and antiseptics. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.) Any Category I ingredient in these groups will be allowed to claim "relief of burning" as designated within the appropriate Category I labeling sections within this document.

3. *Pain.* Pain can occur as an intensely uncomfortable stimulation of the sensory nerve fibers in the anorectal area. Minor degrees of pain may be caused by either irritation or inflammation. The Advisory Review Panel on OTC Internal Analgesic, Antipyretic, and Antirheumatic Drug Products included some cogent observations as published in the **Federal Register** of July 8, 1977 (42 FR 35346) on the nature of pain and why pain defies definition despite the fact that everyone has experienced it. That Panel recognizes, as does this Panel, that minor pain can be distinguised by the consumer and provides a reasonable goal for OTC anorectal drug products. Severe pain in the anoretal area signals conditions that should cause the consumer to consult a physician.

The relief of pain can be obtained by use of local anesthetics, vasoconstrictors, counterirritants, astringents, wound-healing agents, and antiseptics. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.) Any Category I ingredient in these groups will be allowed to claim "relief of pain" as designated within the appropriate Category I labeling sections within this document.

4. *Inflammation.* Inflammation refers to a condition in which the affected tissues have reacted to produce pain, heat, redness, and swelling. It usually is due to infection with a microorganism, allergy, or to undue trauma.

The cause is sometimes difficult for a physician to establish so that specific treatment can be initiated. It is unreasonable for the consumer to be expected to establish the cause of inflammation because specialized knowledge is required and there is the additional obstacle of directly viewing the anorectal area. The consumer can reasonably recognize the symptoms of pain, burning, itching, and swelling, which may result from inflammation or irritation and choose anorectal ingredients that are effective in the temporary relief of these symptoms. The relief of inflammation can be obtained by use of protectants, wound-healing agents, and antiseptics. (See part II. paragrpah F. below—Pharmacologic Groups and Relief of Symptoms.) Any Category I ingredient in these groups will be allowed to claim "relief of inflammation" as designated within the appropriate Category I labeling sections within this document.

5. *Irritation.* Irritation in the anorectal area is a condition resulting from stimulation of nerve endings by various causes. This condition is recognized by the consumer to the exent that it causes pain, burning, itching, or swelling. The relief of irritation can be obtained by use of local anesthetics, protectants, counterirritants, astringents, wound-healing agents, and antiseptics. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.) Any Category I ingredient in these groups will be allowed to claim "relief of irritation" as designated within the appropriate Category I labeling sections within this document.

6. *Swelling.* Swelling represents the temporary enlargement of cells and/or tissue due to excess fluid associated with hemorrhoids or hemorrhoidal tissue. The relief of swelling can be obtained by use of vasoconstrictors, wound-healing agent, and antiseptics. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.) Any Category I ingredient in these groups will be allowed to claim "relief of swelling" as designated within the appropriate Category I labeling sections within this document.

7. *Protrusion.* Protrusion is defined as the appearance of hemorrhoidal or rectal tissue outside the anal canal. It can follow swelling of hemorrhoidal tissue and/or loss of muscular support. This symptom is not treatable by OTC preparations and a physician should be consulted.

8. *Seepage.* Seepage is the leaking of either fecal material and/or mucus from a partly open (incontinent) anal sphincter. It may include the discharge of pus from a fistula or feces through a fistula that connects the rectum to the anal canal. In either case, a physician should be consulted because OTC products are not available for relief of this condition.

9. *Bleeding.* Bleeding is a common symptom of anorectal disease and may indicate malignant disease of the colon and/or rectum. This symptom should never be regarded lightly. The Panel concludes that this symptom must not be treated by OTC preparations. A physician should be consulted so that a complete examination of the individual may be made.

10. *Discomfort.* Discomfort is defined in part by Webster's Third International Dictionary as a "mental or physical uneasiness, less intense and less localized than pain." Discomfort in the anorectal area may refer to any or all of the following symptoms: burning, irritation, itching, pain, or swelling. The relief of discomfort can be obtained by use of local anesthetics, vasoconstrictors, protectants, counterirritants, astringents, wound-healing agents, and antiseptics. (See part II. paragraph F. below—Pharmacologic Groups and Relief of Symptoms.) Any Category I ingredient in these groups will be allowed to claim "relief of discomfort" as designated within the appropriate Category I labeling sections within this document.

F. Pharmacologic Groups and Relief of Symptoms

The Panel wishes to emphasize certain elementary principles. It recommends as a primary approach to relief of symptoms that all OTC anorectal products carry the instructions "When practical, wash the anorectal area with mild soap and warm water and rinse off all soap before application of this product." (See part II. paragraph Q. below-Labeling.) Furthermore, OTC products that are used to relieve the symptoms discussed within this document should be applied or inserted after bowel movements rather than before because in the latter case the effect would be lost.

OTC anorectal ingedients can be classified into several groups on the basis of their pharmacologic action. The anorectal ingredients discussed within this document were classified on the basis of their pharmacologic activity—local anesthetics, vasoconstrictors, protectants, counterirritants, astringents, wound-healing agents, antiseptics, keratolytics, and anticholinergics. As an aid in evaluating the effectiveness of individual OTC anorectal ingredients to relieve the symptoms associated with anorectal disorders, the Panel constructed the following chart in which each pharmacologic group was classified with respect to its effectiveness, generally, in relieving each of the symptoms associated with anorectal disorders, i.e., itching, discomfort, irritation, burning, swelling, pain, inflammation, protrusion, seepage, and bleeding:

Common Symptoms for Which Anorectal Ingredients Are Used and Their Effectiveness

	Local anesthetics	Vasoconstrictors	Protectants	Counterirritants	Astringents	Wound-healing agents,[1]	Antiseptics	Keratolytics	Anticholinergics[2]
Itching	+	+	+	+	+	±	±	+	(−)
Discomfort	+	±	+	+	+	±	±	(−)	(−)
Irritation	+	(−)	+	±	+	±	±	(−)	(−)
Burning	+	(−)	+	±	±	±	±	(−)	(−)
Swelling	(−)	+	(−)	(−)	−	±	±	(−)	(−)
Pain	+	±	(−)	+	+	±	±	(−)	(−)
Inflamation	(−)	(−)	±	(−)	(−)	±	±	(−)	(−)

Protrustion: Labeling not appropriate for OTC products. (See part II. paragraph E.7 above—Protrusion.)
Seepage: Labeling not appropriate for OTC products. (See part II. paragraph E.8 above—Seepage.)
Bleeding: Labeling not appropriate for OTC products. (See part II. paragraph E.9 above—Bleeding.)

[1] All ingredients are Category III.
[2] All ingredients are Category II.
(+) Indicates that symptoms will be relieved (Category I).
(−) Expected not to relieve (Category II).
(±) May relieve (Category III).

The following definitions were developed by the Panel as they apply to the specific pharmacologic groups discussed within this document:

1. *Absorbent.* An agent that takes up within itself fluids or other substances on, or secreted by, the skin or muccous membranes.

2. *Adsorbent.* An agent that because of its fine state of subdivision, is capable of attaching other substances onto its extensive surface area.

3. *Anticholinergic.* An agent that inhibits or prevents the action of acetylcholine, the transmitter of cholinergic nerve impulses.

4. *Antiseptic.* An agent that will inhibit the growth and development of microorganisms but will not necessarily destroy them.

5. *Antipruritic.* An agent that reduces or abolishes the sensation of itching.

6. *Astringent.* An agent that is applied to the skin or mucous membranes for a local, limited, usually reversible, protein-coagulant effect.

7. *Bacteriostat.* An agent that arrests or hinders the growth of bacteria.

8. *Counterirritant.* An agent that produces a local sensation that distracts from the perception of pain, burning, or itching. The perception of these symptoms are distracted and commonly replaced by warmth, cooling, or tingling sensations.

9. *Demulcent.* An agent that forms colloidal solutions and because of its cohesiveness has the capacity to protect skin surfaces in a manner similar to that of mucus.

10. *Emollient.* An agent used to soften or protect internal or external body surfaces.

11. *Emulsifier.* An agent that promotes the uniform distribution of one substance into another.

12. *Germicide.* An agent that kills pathogenic microorganisms and that is intended for use on inanimate objects and surfaces.

13. *Kedratolytic.* An agent that produces desquamation (loosening) and debridement (sloughing) of surface tissue cells of the epidermis.

14. *Local Anesthetic.* An agent that produces temporary local disappearance of pain, burning, itching, discomfort, and/or irritation by reversibly blocking nerve condition when applied to nerve tissue in appropriate concentrations. The term "topical anesthetic" is included by the Panel in this definition.

15. *Lubricant.* An agent that reduces surface tension and friction between two surfaces.

16. *Protectants (includes absorbents, adsorbents, demulcents, and emollients).* Agents that, when applied to the skin or mucous membranes, provide a physical barrier that forms a protective coating over tissues.

17. *Vasoconstrictor.* An agent that causes temporary constriction of the blood vessels.

18. *Vehicle.* A usually inert agent or combination of agents used to confer desirable consistency or form or to serve as a suitable carrier for the active ingredients.

19. *Wound-healing agent.* An agent that increases the rate of healing of a wound compared with the rate of healing of a wound that is untreated or treated only with protectants.

G. *Bioavailability of Anorectal Dosage Forms*

1. *General comment.* The Panel requires final formulation testing based on the following discussion. The Panel concurs with the definition of bioavailability as published in the **Federal Register** of January 7, 1977 (43 FR 1624), which is the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from the drug product and becomes available to the site of drug action. Bioavailability is usually determined by measurement of the concentration of the active drug ingredient or therapeutic moiety, or its metabolites in biologic fluids, or in urine as a function of time, or by an appropriate acute pharmacologic effect.

For most drugs, bioavailability is determined by measuring the active drug in the systemic circulation. Bioavailability of a drug is not related to what occurs after the drug enters the systemic circulation, such as distribution, binding, metabolism, or excretion. These processes influence the concentration of a drug throughout the organism, but they have no bearing on its bioavailability.

The bioavailability of the active ingredient in an OTC anorectal drug product is a function of the physiocochemical properties of the active ingredients but is by no means determined solely by them. The clinical application of the bioavailability concept is not primarily limited to the pharmacologically active ingredients but more so to certain characteristics of the drug products available for therapeutic use under the circumstances of such use. This concept applies to the fact that active ingredients may not be available because of the presence of certain inactive ingredients, and there may be individual variations in anatomy and physiology that will modify bioavailability. Thus, the bioavailability of OTC anorectal drugs is dependent upon the interaction of such characteristics as the physiocochemical properties, the formulation, the manufacturing process of the drug, and physiological factors, as well as upon drug dosage, dosage form, and the site of application (externally or intrarectally). In the case of anorectal absorption, the bioavailability of a drug is determined by its release from its vehicle, its solubility in the rectal fluids, diffusion to the absorbing membrane, and transfer into the body via the vascular bed perfusing the tissue (Ref. 1).

2. *Factors influencing bioavailability*—a. *Physicochemical properties of drugs.* The lipid-water solubility of a drug (lipid-water partition coefficient) must be considered in choosing a base for drugs administered anorectally. A drug which is highly soluble in a fatty base and present in low concentration is slowly released from its base and has only a slight tendency to diffuse into the small amount of aqueous rectal fluid. A drug which is slightly soluble in the fatty base and present in a concentration

close to its saturation will diffuse more readily into the aqueous rectal fluid (Refs. 2 through 5). Thus, water-soluble, oil-insoluble salts, e.g., ephedrine sulfate, are preferred for rapid absorption from a fat-type base, e.g., cocoa butter. For a water-soluble or water-miscible type base, e.g., polyethylene glycol, a water-soluble salt is preferred for more rapid drug absorption. The rate-limiting step in absorption for drugs incorporated in a fatty base seems to be the transfer of the drug from the base to the rectal fluid. In the case of water-soluble or water miscible-bases, the rate-limiting step in absorption seems to be drug transfer through the rectal mucosa (Ref. 3).

The rate of drug release from its base may be increased by increasing the concentration of the active ingredients. However, it appears that after a certain limit is reached any further increase in concentration has little effect on absorption. Absorption of drugs through the anorectal barrier is considered to be a matter of simple diffusion across a permeable membrane. In contrast, diffusion of a drug from its base is a function of the drug's concentration as well as such properties as its solubility in the anorectal fluids, the ionization or dissociation constant of the drug, the dissolution rate of the drug from the dosage form, the pH of the base, the particle size of the drug, and the presence of other ingredients that may interact with the active drug (Refs. 2 and 6).

All of the above factors may greatly affect the actual safety and effectiveness of an anorectal product, and this is the basis on which the Panel requires final formulation testing.

b. *Formulation and manufacture of the drug product.* OTC anorectal drug products are compounded and manufactured by a variety of techniques. Thus, the formulation and manufacturing process can greatly influence the bioavailability of the active ingredient in an anorectal drug product.

In the formulation of suppositories, for example, viscosity-increasing agents or other additives may be necessary to stabilize the physical properties of the suppository, i.e., prevent softening of the base which makes administration difficult or prevent rapid settling of suspended drug particles in melted base, during the molding process (Refs. 3 and 4). The inclusion of surface-active agents is usually necessary in the formulation of anorectal dosage forms, e.g., ointments, creams, and suppositories. Their presence may increase or decrease absorption rate. The surfactant may reduce the surface tension of the mucous blanket that covers the rectal membrane, creating an environment favoring drug absorption. It may also act as a solubilizing agent for the active ingredient, and the solubilized form may be absorbed more readily. By contrast, the surfactant may decrease absorption rate through the formation of a drug-surfactant complex (Refs. 7, 8, and 9). The data available on the relationship of surfactants to drug release and absorption is limited, making predictions difficult.

Drug release and absorption may also be influenced by the manufacturing process. For example, the temperature used for melting cocoa butter, which exhibits marked polymorphism (the property of existing in different crystalline forms), must be carefully controlled. Each polymorphous form of cocoa butter has different melting points as well as different release rates. The formation of the various polymorphous forms of cocoa butter depends upon the degree of heating, on the cooling process, and on various other factors during this process (Refs. 3, 4, and 5).

These variable factors likewise affect overall safety and effectiveness of an individual ingredient and thus further justify the need for final formulation testing.

c. *Physiological factors.* Anorectal physiology may also be a factor affecting anorectal drug absorption. In the absence of fecal matter, the rectum contains a small amount of aqueous fluid with a pH of approximately 7.2, but of very low buffering capacity. Thus, the pH of this rectal fluid may be affected by the drug(s) dissolved in it. The rectal epithelium is lipoidal in nature; hence, it is preferentially permeable to nonionized drugs. The degree to which penetration occurs is a function of the pH and the ionization constant of the drug. Ordinarily, a mucous blanket covers the rectal mucosa of the rectum, and it may impede the diffusion of drugs into the surrounding tissues (Refs. 3 through 6).

The nature of the blood supply to the anorectal region, involving the hepatic and systemic circulation, may also affect overall drug bioavailability. A drug administered rectally may by-pass the liver to enter the systemic circulation, or it may enter the hepatic system where it may undergo modification in activity. The amount of drug absorbed directly into the general circulation depends upon where the drug is released in the rectum. For example, if a suppository remains in the lower part of the rectum, more of the drug will enter the general circulation, circumventing an initial pass through the liver, than will enter if the suppository moves to the upper regions of the rectum where the upper hemorrhoidal veins, which lead to the liver, predominate. Thus, drug bioavailability may be sharply reduced with drugs that undergo significant hepatic degradation (Refs. 3, 4, and 5).

Additional physiological factors that may influence anorectal drug absorption include fecal impaction, colonic obstruction, body dehydration, and diarrhea. Even muscle tone, which influences movement of anorectal fluids and aids in the disperson of dissolved drugs, may be a factor.

In summary, it appears that the rate-limiting factor in rectal absorption is the diffusion or release of the drug from the base (vehicle). Dissolution of the drug is apparently limited by the small amount of rectal fluid available for interaction with the rectal dosage form. The base may be absorbed at varying rates and carry the drug along with it, or the base may coat the mucous membrane to delay or minimize absorption (Ref. 10). Additionally, the physiochemical characteristics of the drug and vehicle and anorectal physiology must also be considered in evaluating the bioavailability of drugs from OTC anorectal drug products (Ref. 11). The Panel recognizes that the effectiveness of topical application of anorectal drug products is affected by the bioavailability of the active ingredient. However, in addition to absorption through the skin, some products are delivered intrarectally. Bioavailability of the active ingredient of such products becomes a concern for reasons of safety due to absorption through the rectal or colonic mucosa with varying degrees of subsequent systemic effects. Therefore, the Panel concludes the final formulation must be tested for safety and effectiveness because testing of individual ingredients cannot predict either safety or effectiveness of an anorectal drug product.

The Panel emphasizes that bioavailability was an important concern in the review and evaluation of each ingredient categorized in this document. The Panel recognizes that there is, at present, a lack of bioavailability data for many of the drugs discussed in this document. However, when available, the existing data were considered in the evaluation of these ingredients. The Panel also recognizes that as more bioavailability data become available some of the recommendations made in this document may need to be altered to conform to the scientific literature and that the appropriate division within FDA

should review the data and institute appropriate changes.

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H. Rectal Absorption

The phenomenon of rectal absorption of drugs has been studied and discussed (Refs. 1 through 4). Despite the complicated nature of the topic, several statements may be made. Generally, in vitro models, though useful, have little relationship to in vivo drug release until correlated to effectiveness (Refs. 1 and 4). Use of in vivo models (rats and dogs) raises the question of relevancy to human rectal absorption.

The degree and rapidity of absorption has been shown to be a function of many factors such as properties of the vehicle (Ref. 4) and concentration of the active ingredents (see part III. below—Local Anesthetics), formulation (Ref. 4), drug properties (Refs. 1 and 4), drug vehicle interaction (Ref. 5), contents of the rectum (Ref. 2), and the mode of transport through the rectal mucosa (Refs. 4 and 6). It also is probably dependent on relative venous pressure in systemic and portal systems, state of rectal mucosa regarding inflammation, pH and body positioning (upright versus supine).

Medication administered intrarectally can be absorbed into the systemic and/or portal circulation within minutes or much more slowly depending on the above mentioned factors (Ref. 1). The absorption may be greater (Refs. 2 and 7), equal to (Ref. 2), or less than (Refs. 2 and 4) oral administration, and is less consistently predictable than by other routes (Ref. 2). Because of the anatomical relationship in this area, drugs absorbed through the rectal mucosa will be absorbed initially into the caval (systemic) or hepatic (portal) circulation or both, whereas oral drugs pass initially into the portal circulation (Refs. 1 and 4).

Therefore, the Panel concludes that the final formulation must be tested for safety and effectiveness because testing of individual ingredients cannot predict either safety or effectiveness of an anorectal drug product.

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I. Anorectal Dosage Forms

1. *General comment.* Anorectal products may be applied in several ways and are manufactured in corresponding forms. For external application, ointments, creams, pastes, gels, liquids, pads, and foam have been used. For intrarectal use, suppositories, introduction of ointment, creams, and gels by pile pipes or by one's finger, and foam via applicators are the common methods. Ointments, gels, suppositories, and foams will be described in more detail below and are also discussed elsewhere in this document. (See part II. paragraph G. above—Bioavailability of anorectal Dosage Forms and part II. paragraph H. above—rectal Absorption.)

A question was raised concerning the use of dusting powders as a dosage form because some of the ingredients, i.e., zinc oxide, have at various times and for various purposes been used in this manner. However, no submissions were received by the Panel to consider this dosage form. It is not discussed any further in this document.

2. *Ointments, creams, gels, jellies, and pastes.* Ointments are semisolid prepartions for external or intrarectal application and are of such consistency that they may be readily applied to the skin by inunction or inserted into the rectum by means of rectal applicators. They should be of such composition that they soften but do not necessarily melt when applied to the body. They serve as vehicles for the topical application of medicinal substances and also function as protectants and emollients for the skin by forming a continuous layer on the surface. Depending on the site of application, the physiochemical properties of the base, and the ingredients incorporated therein, an ointment may simultaneously act as a protectant, emollient, and vehicle (Ref. 1).

For many years, ointments were limited by definition to mixtures of fatty substances. Today, in addition to such oleaginous mixtures, there are preparations of greater efficiency possessing the same general consistency but with an entirely different appearance, such as water-in-oil and oil-in-water emulsions that are also called creams or pastes (Ref. 1). Jellies and gels are usually water-washable or water-soluble. However, because the definition of creams, pastes, gels, jellies, and ointments overlap on certain characteristics, this designation is less meaningful than the ability of a product to be water-washable or water-resistant as discussed elsewhere in this

document. (See part V. below—Protectants.)

Creams and ointments containing large amounts of insoluble powders are referred to as pastes. Pastes are usually stiffer and more absorptive than creams and ointments (Ref. 1).

Ideally, an ointment base should be nonirritating, nondehydrating, nongreasy, compatible with common ingredients, stable, easily removable with water, absorptive (able to absorb water, and/or other liquids), and able to release incorporated ingredients efficiently. No ointment base possesses all of these characteristics (Ref. 1).

Ointments, including creams and pastes, vary in effect and can have a psychological as well as a soothing effect and protectant action on those patients with anorectal disorders. Ointments can be applied externally or intrarectally unless the active ingredients contained in the product limit usage in some way. Because there are no clear differences between ointments, creams, gels, jellies, and pastes, any of these terms are implied whenever the term "ointment" is used in the following discussions.

a. *External application.* Ointments are applied to the perianal area and the anal canal as a thin covering. Amounts can vary but should cover the entire irritated area. Application of large amounts may be wasteful and could cause excessive hydration and softening of the skin (maceration of the tissues).

b. *Intrarectal application.* In addition to suppositories, pile pipes and other mechanical devices have been developed for intrarectal delivery of anorectal preparations. The main advantage of intrarectal application is patient acceptance. The main disadvantage is the possibility of injury. Some patients prefer applying medication by using their fingers. With a properly functioning anal sphincter (which does not allow seepage of rectal contents) the ointment applied by pile pipe has only a brief contact with the skin of the anus and anal canal. Most of the contact is on the rectal mucosa where the highest degree of absorption occurs. Intrarectal administration of anorectal preparations can be accomplished by suppositories or by tubes that pass through the anal sphincter. These pile pipes are of differing designs but their function is 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.

In the presence of a properly functioning anal sphincter it should be expected that, in the rectum, dispersal of the contents of the container of drug will be dependent upon the force exerted by the delivery system (usually a tube and pile pipe) and the location of the holes in the tip of the pile pipe. The pipe must be long enough to pass through the anal sphincter. Lateral openings near the end of the pipe should allow direct contact with internal hemorrhoids and the lowest portion of the rectal mucosa. A hole only in the end combined with strong pressure could result in wide dispersal as high as the upper portion of the rectum leaving relatively little in the hemorrhoidal area, especially if the consumer lies down immediately after application. If the consumer remains in an upright position, the drug product may be expected to remain in contact with the lower rectum due to the force of gravity.

Pile Pipes can be stiff or flexible. Because there is some danger that the mucosa can be perforated if they are not inserted correctly, tips should be well lubricated and preferably flexible to avoid injury. All applicators should be cleaned before and after use. The label of products to be administered by pile pipes should be accompanied by the following warning, "Do not use this product if the introduction into the rectum causes additional pain. Consult a physician promptly." (See part II. paragraph Q.5. below—Warnings.)

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3. *Suppositories.* Suppositories were known to the Assyrians about 2600 B.C. and were later used by the Egyptians, Greeks, and Romans (Ref. 1). Early Egyptian medical records show a variety of anal conditions and multiple remedies for the treatment of local conditions. Suppositories used in Europe today are employed primarily as a delivery mechanism for drugs that act systemically, whereas the use of suppositories in America is both for a local effect and less frequently for systemic effects.

Throughout the centuries, suppositories have been inserted into the rectum for the principal purpose of promoting defecation. During the Middle Ages, fat tallow, candle wax, and soap were employed as suppositories. By 1766, cocoa oil was used in the manufacture of suppositories. In 1888, Dr. Ismar Boas recommended that glycerol suppositories be used for constipation. The rationale was to encourage easier, more comfortable bowel movements. An easier bowel movement is what the person with an anorectal disorder has always welcomed.

For those consumers with anorectal disorders, the suppository has a great psychological effect. It makes the person feel as if something is really being done to cure the disorder when in fact only a temporary relief of symptoms has been achieved. A suppository, with its lubricating properties, in some cases, may ease the passage of feces and may decrease other anorectal symptoms. However, the use of the suppository may delay the person from seeking needed medical or surgical care unless limitations of use are carefully read and followed by the consumer.

With a properly functioning anal sphincter, i.e., one that does not allow seepage of rectal contents, the inserted suppository has only a brief contact with the skin of the anal canal. Most of the contact is on the rectal mucosa where the highest degree of absorption occurs. The commonly manufactured "bullet shaped" suppository, after insertion, leaves the site of pain and moves into the rectum and sigmoid. Only when the suppository melts do the active ingredients become available. Instructions to maintain the upright position may give gravity a better chance for the suppository's active ingredients to alleviate symptoms.

The suggestion has been advanced that the suppository should be shaped preferably like an "hour glass" or "collar button" so that it remains in the anal canal. This concept merits further study.

The Panel is aware of many cases of rectal or colonic cancer (Refs. 2, 3, and 4). The Panel is concerned that reliance upon prolonged suppository use to self-treat symptoms may cause delay in seeking definitive medical care.

Increased education in regard to proper usage of suppositories in anorectal disorders should be promoted.

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4. *Foams.* A specially designed applicator which is claimed to deposit

medication externally (in the anal canal) and in the lower rectum was submitted to the Panel (Ref. 1). The applicator is designed for use with a foam that incorporates the active ingredient. The design of the applicator is intended to overcome the inadequacies of suppositories. As indicated in the above discussion on suppositories, the medication applied to the anal canal is minute as the suppository passes into the rectum. The suppository will travel to the upper rectum if the consumer is prone; is the consumer is erect it will remain the the lower rectum. The ability of foam to remain in the anal canal and the lower rectum will be affected by formulation, which in turn will control the duration of effectiveness of the active ingredient. Therefore, in the opinion of the Panel, it is necessary for each foam product to be tested for effectiveness in final formulation against foam without active ingredient.

It is not reasonable to extrapolate the results of one foam product to another because the mixture of propellant and formulation will effect the size of the bubbles (Refs. 2 and 3). Thus, large bubbles will cause the foam to have a lower concentration of ingredient and smaller bubbles will cause a higher concentration per unit volume. It is important with foams to relate the concentration to a unit volume (ideally, 2 milliliters (mL) which is the volume of approximately 2 grams (g) of water) instead of relating the concentration to a unit of weight as is done with other dosage forms, i.e., suppositories or ointments (ideally, 2 g). The most extreme example of this point would be a single bubble formed by a shell of emulsion that weighs 2 g, with a specific gravity of 1 (for convenience in calculations), which had a useful thickness of 0.65 millimeter (mm). (See part II. paragraph K.3. below—Concept of a 2 g dosage unit and part V. paragraph A. below—General Discussion.) The bubble would have a diameter of approximately 30 mm and a volume of more than 14 mL (slightly larger than a ping pong ball). This calculation makes it clear that foams must relate concentration to volume of the final product because the maximum concentration is achieved when all the bubbles are gone. To substantiate superiority of foam over ointment or any other dosage form, studies that are not currently available must be done.

The proposed ban for the nonessential use of chlorofluorocarbons in products subject to FDA control as published in the **Federal Register** of March 17, 1978 (43 FR 11301) did not exempt anorectal products; therefore, the propellant in such foam-producing products shall have to be other than halogenated hydrocarbons. The sponsor of one product proposed to replace the halogenated hydrocarbon propellant with isobutane. Other propellants may also be available at a later date, but these ingredients are considered pharmaceutical aids and as such are to be considered later in depth by FDA.

The need to produce a foam for delivering the active ingredient is not clear to the Panel. A properly designed ointment applicator should serve the same purpose, but the Panel does not intend to restrict ingenuity in product design provided the product accomplishes the claimed effect. It has been noted that foam cannot contain as much active ingredient per unit volume as can an ointment because of the mixture with the propellant. This may severely restrict the ability of such a dosage form to meet minimum concentration requirements, e.g., if a foam product claims to be a protectant, which must be present as 50 percent of the dose, and only 30 percent can be incorporated in the metered dose. Such a product cannot make protectant claims and would necessitate reformulation and/or relabeling.

Therefore, foam products must meet the same requirements of safety and effectiveness as any other dosage form, and if any advantage is claimed, studies and data must be provided because related studies and data currently available are not sufficient to establish effectiveness (Ref. 2).

The quantity of drug product most likely to produce results and constitute a reasonably useful amount is discussed elsewhere in this document. (See part II. paragraph K.3. below—Concept of a 2-g dosage unit.)

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J. Allergy and Sensitization of the Anorectal Area

Adverse reactions to topical ingredients usually consist of one or more of the following: Photosensitization, sensitization to irritants, allergic reactions, and systemic toxicity (Refs. 1 through 7). Because of present societal attitudes, photosensitization of the anal area is not of importance, and systemic toxicity will be discussed in reference to specific pharmacologic groups, when appropriate, elsewhere in this document.

Allergic, sensitization, or irritative reactions were considered in the process of evaluating the safety and effectiveness of OTC anorectal products. The perianal skin is usually occluded by clothing, and often moisture and increased warmth persist which, in the presence of the many ingredients found in OTC and prescription anorectal products, cause a greater number of adverse reactions than the same products when applied to skin that is dry and not occluded.

Exact incidence of primary irritant or allergenic reactions has not been established and is influenced by various factors (Ref. 3). Many investigators as well as the International Contact Dermatitis Research Group (ICDRG), an outgrowth of the North American and European Contact Dermatitis Research Group (NACDRG and ECDRG), have been executing studies in patch testing and, simultaneously, are attempting to standardize methods of testing and reporting (Refs. 1 and 3 through 6). Stolley (Ref. 2) has stated that approximately 5 percent of all hospital admissions are for varying degrees of adverse reaction to drugs and approximately 15 percent of the patients seeking medical services are admitted for the treatment of adverse reactions (Ref. 2). It is more difficult to establish definite figures for outpatients. Often the symptoms of an adverse reaction to a medication applied to the diseased anorectal area are similar to the symptoms of the disease, so a patient only presumes the medicine is not helping. Studies performed in dermatology clinics are beginning to give more definite estimates of incidence of outpatient reactions (Refs. 1, 3, 4, and 5).

Many OTC anorectal products contain ingredients that may have an allergic or sensitizing potential. In North American and European studies, reactions to balsam of Peru, an ingredient used in some OTC anorectal products, ranged from an incidence of 0.4 to 28 percent (Ref. 6). Cross reaction to other perfumes was also noted because many different types of perfumes are used on OTC anorectal products (Ref. 3). In North America, the widespread availability of topical medications containing local anesthetics is believed to account for the reaction rate of 8.4 percent. Criteria and studies for evaluating allergenic or sensitizing compounds are well-defined (Refs. 1, 3, and 7). Some additional aspects of sensitization and allergy are discussed

elsewhere in this document. (See part V. paragraph B.1.g. below—Lanolin (external and intrarectal use).)

The Panel concludes that, although a certain portion of the population will experience allergic or sensitization reactions from the use of OTC anorectal preparations, in general, these preparations can be used safely without allergic reaction by most individuals at the recommended dosages. In those instances where allergenicity or sensitization from specific ingredients are important considerations for labeling, the Panel has specified an appropriate warning to be included in that ingredient's labeling.

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K. Principles Applicable to Combination Products

1. *General combination policy.* Most anorectal products currently on the market contain ingredients reviewed by the Panel and are promoted or sold to relieve a number of different symptoms. For example, OTC products commonly used for the treatment of the symptoms associated with "hemorrhoids" include ingredients intended to provide relief of one or more concurrent symptoms such as burning, itching, swelling, and pain. These products may contain more than one active ingredient to relieve a spectrum of symptoms.

To clarify the place of combinations in the marketplace, the Panel applied the OTC drug review regulation requirement contained in 21 CFR 330.10(a)(4)(iv) which states 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.

The Panel concurs with the regulation and concludes that each active ingredient in a combination product must contribute to the claimed effects and that each active ingredient must be a necessary component for rational therapy of concurrent symptoms.

The Panel has established specific criteria for the treatment of symptoms with combination products. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group, except for protectants as specified elsewhere in this document. (See part II. paragraph K.6. below—The combination of active ingredients from the same pharmacologic group.)

The Panel has placed combinations of two active ingredients from the same pharmacologic group in Category III, except for protectants. Each active ingredient must be generally recognized as safe and effective when used alone for the claimed effects and must make a contribution to the claimed effects when in combination. Therefore, the Panel has recommended only specific combinations be provided and limited to one active ingredient from any one pharmacologic group except for protectants. The Panel recognizes that in the case of the pharmacologic group of wound-healing agents, it may be rational to include more than one such ingredient in a product because of their different mechanisms of action. However, until proven that each wound-healing ingredient makes a significant contribution to the wound-healing effect of the product, the Panel's statement placing such combination products in Category III applies.

The Panel concludes that combinations of ingredients are safe and effective if they provide rational concurrent therapy for a significant existing target population that can benefit from their use. The Panel emphasizes that these combinations must contain adequate directions for use and include warnings against unsafe use. These combinations of active ingredients must clearly specify in their labeling the anorectal symptoms for which they are indicated.

2. *Requirement that ingredients from different pharmacologic groups contribute to the claimed effects.* The Panel has placed certain ingredients in Category I as safe and effective, based on a review of the literature, data submitted, and clinical expertise. However, if a Category III ingredient is to be raised to Category I, it must be shown that it makes a statistically significant therapeutic contribution to the claimed effects.

The Panel considers the following criteria as providing a rational basis for determining the contribution of each active ingredient in an anorectal preparation: (a) Each active ingredient in a combination has been found to be safe and effective (Category I) and its inclusion clearly contributes to the claimed effects as shown by clinical data, and (b) the dosage of each active ingredient must be within the specified dosage range for its claimed therapeutic effects specified in the ingredient statements elsewhere in this document.

3. *Concept of a 2-g dosage unit.* The identification of an average dosage unit was necessary to establish a basic and acceptable minimum quantity for use that provides a therapeutic effect. In considering anorectal products, the Panel concludes that a 2-g dosage unit is reasonable, but this does not imply that other dosage sizes are not acceptable because size could be related to other factors. An official pharmaceutic compendium states that the average suppository weighs 2 g (Ref. 1). It has been previously shown in studies of anorectal products that patients use an average of 2 g per application of ointment (Ref. 2). The Panel recognizes that exceptions as to dosage unit size do occur, but that the 2-g dosage unit permits the relationship of a safe use concentration to a suitable dosage unit size.

Further justification for the use of an average dosage unit of 2 g is provided by the calculation that such a quantity of ointment with a specific gravity of 1.0 would cover an area 10 cm^2 at a thickness of 2.0 mm. A substance such as petrolatum, with a specific gravity of 0.81 to 0.88, would cover a larger area or provide a thicker layer. This quantity is more than sufficient to provide protectant effect as discussed elsewhere in this document. (See part V. below—Protectants.) Such a quantity would have a total volume of 2 mL, which is also used as a basis for the calculations discussed above for the use of foams. (See part II. paragraph I.4. above—Foams.)

References

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

(2) OTC Volume 120022.

4. *Limitation of ingredients in combination products.* The Panel, while recognizing the need for multiple

ingredients in OTC anorectal preparations, concludes that rational therapy dictates that OTC anorectal preparations available to the consumer should contain as few active ingredients as possible at the minimum dosage level recommended by the Panel as safe and effective.

The Panel recognizes that the presence of concurrent anorectal symptoms may justify the use of more than one active ingredient. Thus, there may be several therapeutic goals such as a need to relieve burning, pain, itching, swelling, or to protect the affected area which may be achieved by combining different ingredients in an effective combination. Additionally, the Panel recognizes the need for several types of ingredients for adequate formulation of such combination products. The pharmacologic groups and the ingredients in these groups that will be permitted in a combination will be dependent upon criteria defined elsewhere in this document. Despite the theoretical rationale of a combination of ingredients that relieves several symptoms simultaneously, the Panel concludes that combining ingredients from more than three pharmacologic groups with or without one or more protectants, increases the risks of interactions and of altering effectiveness of the drug product.

The Panel is also aware of the inclusion of inactive, i.e., nontherapeutic, ingredients in anorectal preparations. These inactive ingredients are used in product formulations for various purposes, e.g., preservatives and perfumes. However, the Panel recommends that the safety of inactive ingredients and the advisability of including them in drug products be reviewed by an appropriate body. The Panel briefly discusses inactive ingredients elsewhere in this document. (See part II. paragraph G. above—Bioavailability of Anorectal Dosage Forms and part II. paragraph P. below—Inactive Ingredients.)

In summary, the Panel recommends that OTC anorectal marketed products contain only those active and inactive ingredients that are essential to the product to accomplish its claimed therapeutic effects.

5. *The combination of active ingredients from different pharmacologic groups.* The panel believes that combinations of Category I active ingredients from different pharmacologic groups offer a reasonable means for relieving concurrent symptoms. The Panel can find little scientific justification for including ingredients from more than three pharmacologic groups in the same product.

The Panel concludes that combining more than three Category I active ingredients, each from a different pharmacologic group, with the exception of protectants, would place the combination in Category III. Before such combinations may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms must be identified.

The Panel also concludes that, in addition to three Category I active ingredients, each from a different pharmacologic group, a combination may contain not more than four Category I protectants as specified elsewhere in this document. (See part II. paragraph K.6.a. below—Protectants.) This exception for protectants is not inconsistent with the philosophy of exposing the consumer to the least number of drugs because the effectiveness of protectants is primilarily due to passive physical properties, providing a wide margin of safety. Chemically active protectants will be identified when special problems are known to exist or are suspected.

6. *The combination of active ingredients from the same pharmacologic group*—a. *Protectants.* The protectants have been excluded from the general rule that no more than one ingredient from each pharmacologic group be used in a Category I combination. In the past, protectants have been regarded primarily as pharmaceutical necessities, e.g., vehicles and stiffening agents. However, the Panel has recognized that the physical properties of these ingredients are often of therapeutic value in the symptomatic treatment of anorectal symptoms. (See part V. below—Protectants.) The Panel concluded that this concept is reasonable because protectants are, in general, safe for OTC use and require few limitations on dosage. Also the physical manipulation of varying quantities of these ingredients is useful in formulating products of a desired consistency, e.g., ointment or suppository.

Some protectant active ingredients also have other pharmacological activities and consequently have been reviewed by the Panel for more than one claimed effect.

The Panel further concludes that to exert a protective effect and to justify a claim for this drug effect when only one protectant is present, it must be present in a combination in a concentration of at least 50 percent of a dosage unit. For those protectant ingredients limited to concentrations of less than 50 percent, the data indicate such ingredients are usually present in combination with other protectant ingredients. In a combination containing two, but not more than four, protectants, the total concentration of all the protectants in the combination must be at least 50 percent of a dosage unit. This concept was based on the Panel's determination of the minimum concentration of a protectant ingredient in a combination that wold provide a protectant effect (i.e., at least 50 percent of a dosage unit) and still permit the addition of other active ingredients (e.g., 20 percent benzocaine) and still allow for inactive ingredients.

It is reasonable to expect that no more than four different Category I protectants will be needed in any one product. Only four products submitted to the Panel had four or more protectant ingredients.

b. *Topical anesthetics, vasoconstrictors, conterirritants, astringents, wound-healing agents, antiseptics, keratolytics, and anticholinergics.* The Panel is concerned with the marketing of combination products containing more than one active ingredient from these pharmacologic groups. Each Category I combination is currently limited to one Category I active ingredient from any one pharmacologic group except for protectants. The Panel can find little scientific justification for combining more than one active ingredient from the same pharmacologic group in the same combination product.

The Panel believes that to provide for combinations containing ingredients from the same pharmacologic group would contribute to the likelihood of undersirable additive or synergistic effects. Further, to include in a combination product more than one ingredient from the same pharmacologic group is unreasonable because the use of more than one safe and effective active ingredient serves no added benefit nor decreases the risk of toxic effects. It is accepted medical practice to administer only those drugs necessary for the safe and effective treatment of the patient. The Panel believes that this concept should also apply to self-medication using OTC drugs for relief of symptoms without the advice of a physician.

In conclusion, to allow for the possibility, however unlikely, that there may be advantages to combining two ingredients from the same pharmacologic group, each at less than the recommended Category I dosage, the Panel has determined that such combinations be classified as Category

III. Additional studies are needed for Category III combinations to determine their safety and effectiveness. (See part II. paragraph K.10. below—Criteria for Category III combination products for external and/or intrarectal use.) The Panel has futher determined that any combination product containing more than two active ingredients from the same pharmacologic group, e.g., three vasoconstrictors, is irrational and is therefore classified as a Category II combination. There is no reason to expect a possible benefit from the combintion, and exposure to greater numbers of ingredients may increase the risk of adverse reactions, may decrease safety, and/or may produce unpredictable changes in effectiveness.

7. *Labeling of active ingredients.* As discussed above, the Panel has determined that each active ingredient in a combination product must make a contribution to the claimed effects. (See part II. paragraph K.1. above—General combination policy.) If a single ingredient has more than one pharmacologic activity related to use in anorectal disease, these should all be identified in the labeling and be consistent with the pharmacologic activities produced at the recommended dosage for the combination product.

The Panel recommends that the labeling of a combination product containing active ingredients for treatment of concurrent symptoms emphasize the use of the product only when all such symptoms are present. The consumer should be adequately informed by means of the labeling as to the therapeutic capabilities of the product.

8. *Criteria for Category I combination products for external and/or intraectal use.* Based upon an evaluation of the ingredients and the data submitted to the Panel for review, the following criteria have been established:

a. Each active ingredient in a combination must meet the Category I conditions established within this document.

b. Any Category I combination containing only protectants and claiming a protectant activity may contain no more than four protectants, provided the total concentration of protectants are present in at least 50 percent of the dosage unit. Final testing is not required.

c. Any Category I combination claiming a protectant activity may contain no more than four protectants in addition to the specific combinations of Category I ingredients as set forth below, provided the protectants are present in a total concentration of at least 50 percent of a dosage unit, or, when only one protectant is present in a combination claiming a protectant activity, it must be present in a concentration of at least 50 percent of a dosage unit. (See part II. paragraph K.10. below—Criteria for Category III combination products for external and/or intrarectal use.)

d. 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. (See part II. paragraph K.10. below—Criteria for Category III combination products for external and/or intrarectal use.)

9. *Criteria for Category II combination products for external and/or intrarectal use.* a. A combination is Category II if a Category II ingredient or Category II labeling is present in the combination product.

b. If a combination contains an active ingredient or has labeling that has not been reviewed by this Panel, such ingredient or labeling is classified as Category II.

c. A combination product is classified as Category II if it includes more than two active ingredients from the same pharmacologic group, except protectants.

d. If a combination contains five or more active ingredients, excluding protectants, such a combination is classified as Categry II. It is irrational and presents an increased, unacceptable risk of adverse reactions.

e. Specific combinations of certain pharmacologic groups have been determined by the Panel to be unsafe or irrational and classified as Category II.

(1) Any combination containing both a local anesthetic and a counterirritant. The Panel concludes that the simultaneous use of a counterirritant and a local anesthetic comprises a specific combination that is irrational and is therefore not allowed. The mechanism of action of a counterirritant is dependent upon intact nerve function that is specifically blocked by an effective local anesthetic. Although the onset of action of the local anesthetic may be briefly preceded by the action of the counterirritant, this does not constitute a significant justification for the combination.

10. *Criteria for Category III combination products for external and/or intrarectal use.* Based upon an evaluation of the data submitted to the Panel for review, the following criteria and testing procedures are recommended:

a. If a combination product contains not more than three Category I ingredients each from a different pharmacologic group, excluding protectants, and the final formulation has not been tested for safety and effectiveness, the combination is classified as Category III. The following specific combinations of pharmacologic groups, are in Category III.

(1) Combinations containing any single Category I active ingredient and one or more protectants.

(2) Combinations of any two Category I active ingredients, each from a different pharmacologic group listed below, may be combined with or without one, but not more than four, protectants. (See part II. paragraph K.6.a. above—Protectants.)

(i) Combinations containing a local anesthetic and a vasoconstrictor.

(ii) Combinations containing a local anesthetic and an astringent.

(iii) Combinations containing a local anesthetic and a keratolytic.

(iv) Combinations containing a vasoconstrictor and an astringent.

(v) Combinations containing a counterirritant and an astringent.

(vi) Combinations containing a counterirritant and a keratolytic.

(vii) Combinations containing an astringent and a keratolytic.

(3) Combinations of any of the following three Category I active ingredients, each from a different pharmacologic classification, may be combined with or without one, but not more than four, protectants. (See part II. paragraph K.6.a. above—Protectants.)

(i) Combinations containing a local anesthetic, a vasoconstrictor, and an astringent.

(ii) Combinations containing a local anesthetic, astringent, and keratolytic.

(iii) Combinations containing a vasoconstrictor, counterirritant, and astringent.

(iv) Combinations containing a counterirritant, astringent, and keratolytic.

(4) Category III testing: The above Category III combinations must be subjected to testing before they will be allowed on the OTC market. (See part II. paragraph L. below—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

a. If a Category III ingredient or labeling is present in a combination product containing no Category II

ingredient or labeling, the combination is classified as Category III.

b. A combination product is classified as Category III if it contains four Category I active ingredients, each from a different pharmacologic group, except protectants.

Combinations with ingredients representing four pharmacologic groups are more likely to be less safe and effective than three ingredients. It is not reasonable to assume that a target population exists that requires relief of anorectal symptoms by four different mechanisms. In any case the benefit-to-risk ratio decreases to a questionable level.

Category III testing: If, when tested alone, the Category III ingredient can be shown to be safe and effective in accordance with the standards for evaluation in the recommended protocol, the ingredient then qualifies for Category I status. (See part II. paragraph L. below—Criteria and Testing Guidelines for Placing Category III Ingedients, Combinations, and Labeling in Category I.) The combination will then contain only Category I ingredients, but further testing is required to show that the combination in final formulation is safe and effective.

d. A combination product is classified as Category III even if it contains Category I ingredients from different pharmacologic groups when any ingredient or ingredients used to relieve the same symptom are present at less than the minimum effective dose established by the Panel.

Category III testing: For a Category III combination, testing must be carried out to demonstrate (a) safety no less than that of the individual ingredients and (b) a contribution by each ingredient to the effectiveness of the product.

Testing for effectiveness of all anorectal ingredients and combinations in final formulations should demonstrate in clinical trials that there is 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; e.g., a product composed of active ingredients A, B, C, and D in a vehicle (final formulation) must be compared to control (vehicle plus protectants when present) and the following combinations: (A, B, C), (A, B, D), (B, C, D), and (C, D, A). The combination of other anorectal active ingredients with protectants resulting in unpredictable changes in safety and effectiveness is demonstrated by many investigators (Refs. 1 and 2). For this reason, the formulation of protectants used in testing must be consistently used in each permutation and identified by name and concentration in the monograph. Any change in formulation of protectants used requires retesting.

The exclusion of protectants from testing for relief of irritation, discomfort, burning, itching, or swelling (i.e., Category I claims) does not preclude the need for testing protectants for other claims (Category III), such as zinc oxide when labeled as an astringent.

References

(1) Ritschel, W. A., "Biopharmaceutical Development and Evaluation of Rectal Dosage Forms," *in* "Applied Biopharmaceutics II," College of Pharmacy, University of Cincinnati, Cincinnati, OH, pp. 1153–1207, 1973.

(2) OTC Volume 120072, pp. 5–18.

e. Combinations containing Category III and Category I active ingredients for which the available effectiveness data are insufficient for Panel to make a final determination are classified as Category III and are listed below. Such combinations include Category I and Category III active ingredients on the basis that a theoretical rationale exists for these combinations but safety and effectiveness remains to be established.

(1) Wound-healing agent and local anesthetic.

(2) Wound-healing agent and vasoconstrictor.

(3) Wound-healing agent and astringent.

(4) Wound-healing agent and antiseptic.

(5) Wound-healing agent, local anesthetic, and vasoconstrictor.

(6) Wound-healing agent, local anesthetic, and antiseptic.

(7) Wound-healing agent, vasoconstrictor, and antiseptic.

(8) Wound-healing agent, local anesthetic, and astringent.

(9) Wound-healing agent, vasoconstrictor, and astringent.

(10) Wound-healing agent, astringent, and antiseptic.

(11) Local anesthetic and astringent.

Category III testing: An acceptable testing procedure will be one in which the combination, as well as each individual ingredient of the dose in the combination, and a control (vehicle and protectants when present) are evaluated against the relevant symptoms either in the same study or in separate studies using comparable test protocols. (See part II. paragraph L. below—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.) In this way, comparisons of effectiveness can be made between the combination, the individual active ingredients, and the placebo by external or intrarectal administration. When tested alone by external or intrarectal administration, each individual ingredient should demonstrate a statistically significant effect against the relevant symptom when compared to control (vehicle plus protectants when present).

For the combination of Category I ingredients from different pharmacologic groups to be a Category I combination, the combination must also exert a statistically significant effect against each of the relevant symptoms when compared with the control.

L. *Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I*

1. *General considerations.* The Panel has placed ingredients, combinations, and labeling in Category III because there was insufficient evidence to establish safety and/or effectiveness of the ingredient or combinations when used externally and/or intrarectally for the relief of symptoms associated with anorectal disease. In addition, the Panel concludes that final formulation testing of all ingredients and combinations cannot be avoided.

The Panel has recognized that the testing of a Category III ingredient or combination currently marketed for use in anorectal disorders would necessarily be less rigorous than testing of a new ingredient or combination. This is true, in most cases, because there has been long-term use of the combination products in Category III without any recognized hazard, and it is often necessary to test only one aspect of safety and/or effectiveness for each ingredient or combination. Therefore, rigorous safety testing has been modified to take into account years of human use and experience. Required testing guidelines for all Category III ingredients and combinations are discussed here in general. Specific requirements for each ingredient are identified below and in each individual ingredient section when applicable. A general scheme for evaluation of new anorectal drugs is discussed elsewhere in this document because testing standards adequate to change the classification of Category III ingredients to Category I would not suffice for a new drug entity. The following guidelines pertain to Category III ingredients and combinations of Category I and III ingredients only:

a. *The need for studies in the anorectum.* In all effectiveness studies, the site of study should be the human rectum and anorectal area because of the unique anatomy and physiology of the anorectal area and because the area is frequently traumatized by bowel

movements, ambulation, or pressure while sitting. In addition, the anorectal area is warm and moist because it is usually covered by clothing. These factors make the anorectal area subject to irritation. Other anatomical sites demonstrating the effectiveness of agents for relief of symptoms or for promoting healing are not satisfactory. The Panel has reviewed a variety of clinical studies designed to test the effectiveness of products when used in the human anorectal area (Refs. 1 through 21). These studies confirm both the feasibility of such studies and the availability of patients for such studies. Testing for sensitization and irritation may be done on other skin areas, such as the back or the forearm according to standard tests. (See part II. paragraph L.2.b. below—Safety testing for external use.) Carefully designed trials in humans can simultaneously study allergenicity, local and systemic toxicity, and effectiveness. In most cases safety testing can be conducted on the human anorectal area, but where there is clear concern for systemic toxicity, preliminary animal testing may be necessary.

References

(1) OTC Volume 120003.
(2) OTC Volume 120004.
(3) OTC Volume 120007.
(4) OTC Volume 120008.
(5) OTC Volume 120010.
(6) OTC Volume 120014.
(7) OTC Volume 120015.
(8) OTC Volume 120020.
(9) OTC Volume 120022.
(10) OTC Volume 120023.
(11) OTC Volume 120024.
(12) OTC Volume 120028.
(13) OTC Volume 120030.
(14) OTC Volume 120031.
(15) OTC Volume 120035.
(16) OTC Volume 120037.
(17) OTC Volume 120059.
(18) OTC Volume 120063.
(19) OTC Volume 120065.
(20) OTC Volume 120075.
(21) OTC Volume 120067.

b. *The vehicle as a control.* The ingredient or ingredients should be tested in the vehicle in which they are to be commercially formulated. This requirement is of prime importance because of the complex effects the vehicle may have on ingredient activity and absorption, as discussed elsewhere in this document. (See part II. paragraph G. above—Bioavailability of Anorectal Dosage Forms.) An important example of the effects of vehicle on ingredients is discussed by the Advisory Review Panel on OTC Antimicrobial Drug Products in their evaluation of iodine as an antimicrobial agent as published in the **Federal Register** of September 13, 1974 (39 FR 33103 at page 33129) in which the Panel concludes that the amount of free elemental iodine is an inverse function of complexation with the vehicle which decreases toxicity and effectiveness.

c. *Double-blind studies.* The effectiveness of the ingredient must be tested in human subjects with anorectal disease using a controlled double-blind study. Double-blind trials are necessary because of the extreme variability of the pathology, the course and symptomatology of anorectal disease, and also because of the difficulty in establishing adequte objective methods of assessment. A double-blind trial is best suited for this type of situation because these variables are controlled.

Double-blind trials permit a reasonable basis for assessment of symptomatic relief, which is the primary purpose for using OTC anorectal ingredients. Assessment of symptomatic relief shall be done by questionnaires. Pathology may be evaluated by use of photography and/or biopsy and/or physician evaluation. Biopsy may only be appropriate in certain circumstances. Ideally, clinical trials should include the following groups: (1) A final formulation, including protectants when present, with any ancillary measures specified in the protocol; (2) the vehicle, including protectants when present, without other active ingredients but with any ancillary measures specified in the protocol; (3) ancillary measures only; and (4) no treatment.

Because of the usual progression in the healing of benign anorectal ailments, a crossover design study would not be satisfactory. Therefore, only the first two groups above ((1) and (2)) could be studied in double-blind fashion. Data on the remaining two groups above ((3) and (4)) are very useful, but once established provide a valuable baseline for proof of effectiveness.

Demonstration of statistically significant relief of the symptoms of burning, pain, or itch, and/or resolution of anorectal swelling of hemorrhoids or anorectal tissue as shown by photography and/or biopsy and/or physician evaluation in such trials would provide adequate proof of effectiveness.

The feasibility of double-blind studies of anorectal products in the human has been previously demonstrated in several studies presented to the Panel. Further, a recent, detailed double-blind protocol for thorough testing of anorectal products using some of these anorectal ingredients and other ingredients has also been submitted to FDA (Ref. 1).

Reference.

(1) OTC Volume 120071.

d. *Dose and frequency.* When testing for effectiveness in humans, the ingredient should be applied in doses and in a dosage frequency that is reasonable comparable to actual OTC use. For safety testing, the ingredient should be applied in doses and at frequencies that are twice those used OTC because the Panel recognizes the occasional tendency to overuse anorectal products. It has been shown in studies of intrarectal creams and ointments that an average of 2 g of cream or ointment is used per application (Ref. 1) and that the average suppository weighs 2 g (Ref. 2). The usual number of daily applications is three to four. Therefore, human testing should be carried out for a minimum of 7 days using 2 g four and eight times daily and 4 g four and eight times daily. This regimen will, therefore, test usages of twice and four times the recommended amount. When the ingredient is to be applied intrarectally, the ingredient and the control vehicle must be applied in a quantitative manner by use of a pile pipe or suppository. When applied externally, the ingredient must also be applied in a specified and measured quantity.

References

(1) OTC Volume 120022.
(2) "The United States Pharmacopeia," 19th Rev., The United States Pharmacopeial Convention, Inc., Rockville, MD, p. 704, 1975.

e. *Assessment of subjective and pharmacologic effects.* Testing shall be carried out in patients receiving a final formulation versus control to prove symptomatic relief. For subjective assessment, the use of a questionnaire shall be adequate to demonstrate statistically significant symptomatic improvement, and would be acceptable for proof of claims of symptomatic relief.

The exact format of a questionnaire, in the opinion of the Panel, does not need to be included here, nor does it seem appropriate to do so. A number of studies submitted included variations that could serve as possible models for such a questionnaire (Ref. 1). A standard form should be developed by FDA with the help of interested individuals which will provide a uniform basis for evaluation of improvement in the symptoms of burning, pain, itch, swelling (as in hemorrhoids and/or hemorrhoidal tissue) and discomfort due to these symptoms.

Although the Panel has approved many ingredients on the basis of specific pharmacological activities (anesthesia, counterirritation, or vasoconstriction) demonstrated at other sites in the body, studies demonstrating these specific activities must be performed in the

...a and at the same ...ion and formulation to prove ...im relating to these activities. ...ffects of such anorectal ingredients a... being measured in terms of specific pharmacologic action and/or the general anorectal symptoms.

Reference

(1) OTC Volume 120071.

f. *Statistically significant results*—(1) *General safety considerations.* Because of the considerable differences in the two general areas of application of an anorectal product, i.e., inside and outside the rectum, the safety of these products has been considered on both sites. (See part II. paragraph L.2. below—Safety testing.) Thus, the safety of a product applied intrarectally will relate to its effects on, and absorption across, the mucous membrane lining the rectum. The safety of an externally applied product will relate to its application to normal and inflamed epithelium of the anal canal and perianal area.

All tests for safety shall be carried out using an adequate number of trials in animals or humans to allow adequate statistical analysis, and the results must be statistically significant to be acceptable.

(2) *General effectiveness considerations.* The spectrum of anorectal pathology is broad, but these conditions usually cause a narrow range of complaints due to irritation of sensory nerve endings in the area. This results in, depending on the degree of irritation, burning or pain with or without defecation, tenesmus, or the repeated sensation of the need to defecate, and pruritus or itching of the anal canal and perianal area. Swelling of hemorrhoidal vessels and tissues, which occur for various reasons, are frequently part of the anorectal pathology.

Effectiveness of anorectal products shall be evaluated on the basis of their ability to provide relief of symptoms and/or to produce objective improvement in anorectal pathology within the recommended dosage and frequency.

(i) *Relief of symptoms.* Agents acting to alleviate symptoms act by one of several mechanisms: (*a*) Blockade of sensory nerve sensation, as with local anesthetics; (*b*) production of sensation of a different character, e.g., cooling, which distracts from the original sensation, e.g., pain, as with counterirritants; or (*c*) decreased swelling of affected areas such as hemorrhoids and hemorrhoidal tissues, as theoretically occurs with vasoconstrictors.

It is important to note that agents providing relief by the first two mechanisms, local anesthesia and counterirritation, can only act in external areas (perianal) supplied by sensory nerves, below the anorectal line. However, it has been argued that effects of these agents on the automatic nerves above the anorectal line may provide relief of symptoms as reported in studies with some anorectal ingredients (Ref. 1). Therefore, demonstration of statistically significant relief of symptoms after one or more intrarectal applications, and the duration of effect in two double-blind studies of the ingredient as finally formulated would constitute proof of its effectiveness when performed by separate investigators. Other specific aspects of effectiveness are discussed elsewhere in this document. (See part II. paragraph L.3. below—Testing for effectiveness.)

Essentially no clinical data exist to demonstrate the actual validity of these mechanisms in relieving anorectal symptoms. The Panel has concluded that studies for effectiveness of anorectal ingredients which are performed on other body sites cannot be extrapolated as effective in relieving anorectal symptoms because there is a valid impediment. For example, the lack of pain receptors in the rectum in evaluating local anesthetics and the unique anatomy of swollen hemorrhoidal tissue require specific studies.

The Panel has defined prompt or immediate relief of symptoms as those effects that occur within 20 minutes after application of an anorectal product and have a duration of effect as established by appropriate studies.

(ii) *Other aspects of relief of symptoms.* The Panel concludes that some ingredients and ancillary measures, such as frequent warm water baths (sitz baths), regular cleansing of the anorectal area, although not particularly effective in providing more immediate symptomatic relief, will provide relief within 7 days or less by providing better conditions for healing of the anorectal area, or possibly, actually promoting more rapid healing of the area, and thus secondarily relieving symptoms over a period of time. This effect may occur through several mechanisms.

(*a*) *Maintenance of relative cleanliness or decreased bacterial contamination of the anorectal area.* The Panel concludes that although complete antisepsis in this area cannot be maintained, it is generally recognized that healing is more likely to occur in a relatively clean area. This is accomplished by sitting in sitz baths and/or by washing with soap and water, and careful rinsing of soap. Antiseptics may reduce microbial flora in the anorectal area, but further studies are necessary to show that antiseptics are more effective than soap and water.

(*b*) *Debridement of the affected area.* Certain agents such as keratolytics, as well as soap and water, will remove the necrotic or irritated dead skin cells and thus provide better conditions for regrowth of normal tissue. Such an action is generally believed to allow normal healing and, consequently, relief of one or more anorectal symptoms. Keratolytics are discussed in more detail elsewhere in this document. (See part X. below—Keratolytics.)

(*c*) *Promotion of healing.* It is proposed by several investigators that certain agents may actually stimulate healing in a wounded or inflamed area so that repair is more rapid than normal (Ref. 2). This matter is discussed elsewhere in this document. (See part VIII. paragraph A. below—General Discussion.)

Claims for relief may include the specific pharmacologic group by which an agent provides relief, e.g., local anesthesia, or they may be less specific by claiming that they provide relief of burning, pain, itch, or swelling, except that to be able to make specific claims, such as promoting antisepsis of the anorectal area or healing, evidence of such effects must be produced in addition to general demonstration of relief. If no such claim is desired, demonstration of relief by methods described elsewhere in this document will provide for elevating an ingredient to Category I for relief of symptoms only. (See part II. paragraph L.1. above—Assessment of subjective and pharmacoligic effects.)

References

(1) OTC Volumes 120010 and 120011.

(2) OTC Volumes 120007, 120008, 120009, 120021, 120032, 120060, 120061, 120062, 120069, and 120082.

2. *Safety testing.* A general protocol for testing the safety of anorectal products must be divided into local effects on the skin and mucous membranes, systemic effects of the agency when absorbed from specific dosage forms and formulations, effects to be evaluated on the intact surface as opposed to the inflamed or excoriated surface, the allergy-producing potential through local or systemic routes, and acute and chronic toxicity testing on skin, mucous membranes, and/or specific organs when the ingredient is determined to have systemic effects. A scheme outlining a general protocol for

testing the safety of anorectal products is presented below.

Ingredients in Category III need not be tested at the recommended dosage level for local and systemic safety in animals, in view of their years of use, except when special problems have been identified in the discussion of specific ingredients in this document.

If prior toxicity studies at ten times the concentration recommended for the proposed use of the ingredient have demonstrated a hazard in two species of animals, safety testing must be conducted at the amount and concentration recommended for the proposed use as well as at twice the amount in the same concentration, to allow an estimation of the safety margin in humans. Because of long-standing OTC use without reported toxicity, vigorous animal testing of the ingredient will not usually be necessary except when specified. If significant toxicity is encountered with the higher amount, the ingredient will not be allowed for use at the proposed concentration, and further testing of the ingredient for the specific margin of safety and effectiveness at a lower concentration must be conducted.

Proof of safety is to be determined in humans according to site of use, i.e., intrarectal or external. Testing should include acute and chronic toxicity studies only where the ingredient has been placed in Category III for reasons of safety.

a. *Safety testing for intrarectal use*—(1) *Systemic toxicity.* Some compounds used in OTC anorectal products have been shown to be absorbed when applied intrarectally (Refs. 1 and 2). Compounds for intrarectal use placed in Category III for reasons of safety must be tested for potential systemic absorption from the rectum. Assessment of the absorption shall be made by blood level determinations, or if this is not feasible, by urinalysis and/or physiological measurements. Any ingredient that is shown to be absorbed and that has known direct pharmacologic effects, such as a potential change in vital signs, must have these effects measured simultaneously with blood level measurements. These studies must also include measurements of liver, renal, and hematologic function following exposure to the drug.

When systemic absorption occurs from the rectal mucosa, additional animal studies will be required and reviewed before elevation to Category I. These additional animal studies include (i) carcinogenicity studies where the ingredient resembles known carcinogens or co-carcinogens, (ii) mutagenicity and teratogenicity studies that are of primary importance owing to the frequent use of hemorrhoidal agents in pregnant women, and (iii) pharmacokinetic studies in which the minimal requirement is the demonstration of the half-life of the ingredient and of any major metabolites to demonstrate lack of accumulation in the body.

(2) *Local toxicity.* Testing of the ingredients for rectal irritation shall be done on normal human volunteers and normal rectal mucosa. Assessment may be done by either anoscopic or proctosigmoidoscopic examination and the use of photography and/or a clinical grading system. Assessment can also be carried out by rectal biopsy. If there is significant concern regarding irritancy, these studies may be preceded by conventional patch testing at other body sites in humans or by testing in the rectal area of animals (Ref. 3). However, final proof of lack of irritancy must be made in the human rectum. This is feasible as a part of other clinical studies of the product using a 0 to 3 grading system for patch testing in which 0 is no reaction, 1 is mild erythema, 2 is moderate erythema without exudation, and 3 is severe erythema, exudation, and blistering. If irritation occurs in more than 5 percent of the subjects with an average of less than 2, a warning would be required in the labeling of the product to alert the consumer to the possibility of irritation, as, for example, occurs with resorcinol, but this would not prevent its elevation to Category I. The presence of moderate irritation, e.g., an average of 2 or greater in more than 5 percent of the subjects, would automatically move the ingredient at that dose or concentration to Category II.

The Panel will not require testing for the occurrence of rectal sensitization because allergic reactions on mucous membranes do not appear to be a problem.

b. *Safety testing for external use*—(1) *Systemic toxicity.* The Panel recognizes that there is some potential systemic absorption of ingredients through inflamed perianal and anal canal skin. However, the Panel does not believe this is of sufficient significance to require systemic toxicity testing.

(2) *Local tocicity*—(i) *Irritation.* Some ingredients used in OTC anorectal products may produce significant local irritation with either acute or repeated use. Because these products have long-standing human use with few reports of irritation, studies may be limited to human subjects. Irritation in human subjects may be assessed on the abraded skin, or by patch testing in the anorectal area or on the back. If any irritation occurs on the back (1 or greater) in more than 5 percent of the subjects, studies must then be conducted in the anal canal and perianal area to show lack of similar irritation to move a Category III ingredient to Category I. If less than moderate (average of less than 2) irritation is demonstrated in the anorectal area, this would require a warning in the labeling of the product. If moderate (an average of 2 or greater) irritation occurs in more than 5 percent of subjects, the ingredient will automatically become Category II.

(ii) *Sensitization.* Several ingredients in Category III have known allergenic properties. For these ingredients, where concern about allergenicity is part of the concern about safety, testing should be carried out by standard techniques as described by Draize (Ref. 4) or other standard sensitization tests (Ref. 3).

In clinical trials, no fewer than 200 individuals should be used for estimation of allergenicity. The Panel concludes that an incidence of greater than 3 percent of allergic reactions in a random population, or 10 percent in a dermatologic clinic population in such trials, would place the ingredient in Category II.

References

(1) OTC Volumes 120010 and 120011.

(2) OTC Volume 120027.

(3) Marzulli, F. N. and H. I. Maibach, "Contact Allergy: Predictive Testing in Man," *Contact Dermatitis*, 2:1–17, 1976.

(4) Draize, J. H., G. Woodard and H. O. Calvery, "Methods for the Study of Irritation and Toxicity of Substances Applied Topically to the Skin and Mucous Membranes," *Journal of Pharmacology and Experimental Therapeutics*, 82:377–390, 1944.

3. *Testing for effectiveness.* To elevate an ingredient from Category III to Category I, one of two following effects must be shown:

(1) *Immediate relief of symptoms.* Certain ingredients, such as the local anesthetics and counterirritants, can produce relief of burning, pain, or itching shortly (within 20 minutes) after application. This effect can only be assessed by carefully controlled, double-blind tests of subjective effects in humans with anorectal symptoms. Demonstration of statistically significant relief of discomfort due to burning, pain, itch, or swelling within 20 minutes is sufficient to establish effectiveness. Claims for immediate relief are permitted when testing has been done to prove such relief.

(2) *Relief of burning, pain, itching, or swelling with repeated application.* The Panel recognizes that certain agents, such as protectants, astringents, keratolytics, and wound-healing agents

may provide relief when used after repeated applications over a period of days. The Panel will only consider effects occurring within 7 days, because use beyond this time indicates the need for a physician's evaluation. Clinical studies to prove effectiveness of this type of ingredient must provide statistically significant relief of symptoms greater than control within 7 days.

Claims that specify the time required for the onset and the duration of the relief of symptoms and/or specify the mechanism of action must be substantiated by appropriate testing.

Proof of effectiveness is to be determined in double-blind studies on humans according to site of use, i.e., intrarectal or external, and the duration of treatment. The human subjects must have anorectal disease and associated symptoms.

(i) *Effectiveness testing for intrarectal use.* To provide evidence for relief of symptoms, double-blind tests should be carried out in patients using active ingredients in final formulation versus control (vehicle, with protectants when present). The final formulation must be administered intrarectally only by use of a suppository, pile pipe, or other method that allows quantitative measure. The assessment of relief must be based on subjective and/or objective responses from the consumer by use of a properly designed questionnaire. In addition, a screening technique as proposed by Adriani and Zepernick (Ref. 1) and Riegelman (Ref. 2) may be developed into an objective protocol capable of completion in a short period of time. The technique utilizes blockage of a minute electrical stimulation to skin after application of ingredients to be tested.

Criteria for effectiveness after repeated applications include both symptomatic relief and, optionally, reversal of pathological changes within 7 days.

Relief may occur after repeated applications in the intrarectal area. This theoretically will occur only when pathological changes are reversed. Therefore, relief must be demonstrated by either subjective assessment by questionnaire and/or optionally by objective proof that pathological changes have been reversed.

The definitive proof for reversal of pathological change must be carried out in the human anorectal area by demonstrating clinically accelerated healing of a defined anorectal lesion by biopsy, photography, or clinical assessment in double-blind trials comparing the final formulation with control. Demonstrating this property at other anatomical sites is not adequate to support a claim for effectiveness in the unique anatomical area of the anorectum. A claim specifying wound healing as the mechanism of action of an ingredient can only be made on the basis of appropriate studies, but a claim without reference to the mechanism of action could be made for relief of anorectal symptoms after repeated applications if anorectal studies have demonstrated this.

(ii) *Effectiveness testing for external use.* To provide evidence for relief of symptoms, testing should be carried out as described in paragraph (i) above. Because the endpoint of testing is subjective relief, the only difference in testing design is a dosage form for external use and the site of application.

Criteria for effectiveness include both symptomatic relief after repeated application and the reversal of pathologic changes, such as decrease in inflammation. The relief of symptoms must be demonstrated whether the objective reversal of pathological changes occur or not.

Relief after repeated external application may occur as a result of one or more mechanisms, such as local anesthetics, wound healing, astringency, keratolysis and antisepsis. Evidence of symptomatic relief may be assessed by an appropriately designed questionnaire that does not require that a physician evaluate symptomatic relief.

References

(1) Adriani, J. and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association,* 188:711–716, 1964.

(2) Riegelman, R. H., "An Objective Method for the Evaluation of Topical Anesthesia in the Anorectal Area," *American Journal of Proctology,* 17:402–404, 1966.

4. *Testing for specific claims.* To prove specific claims for wound healing, keratolysis, astringency, and antisepsis, testing must be carried out. However, statistical proof of clinical subjective relief after repeated application must be demonstrated in all cases; this requirement exists to preclude the use of single doses to establish effectiveness.

a. *Wound healing.* (See part VIII. paragraph C. below—Data required for evaluation.)

b. *Keratolysis.* Proof of keratolytic activity by an ingredient in the anorectal area would be difficult to demonstrate except by use of biopsy of the affected skin before and after use of the ingredient. Therefore, such testing may be performed on other body sites. If testing done on other body sites demonstrated clear desquamation of epithelium and necrotic tissue by histological examination (which is feasible), a claim for keratolysis could be made for the ingredient, but the ingredient must be shown to provide symptomatic relief in human double-blind testing.

c. *Antisepsis.* (See part IX. paragraph C. below—Data Required for Evaluation.)

d. *Astringency.* The property of astringency is a variably defined one for which no specific testing methods for effectiveness have been developed. If a claim for such an effect is desired, the method for proof of the effect will be evaluated by FDA at the time of submission.

M. The Pharmacist as a Direct Contributor to Medical Care

The Panel is aware of the current policy as established by the Commissioner in the **Federal Register** of June 4, 1974 (39 FR 19880) which does not presently permit the use of the term "pharmacist" on OTC drug labeling. However, the pharmacist is an integral part of consumer education and deserves to be recognized as a readily available source of drug information.

N. The Use of Anorectal Drugs During Pregnancy and by Nursing Mothers

The incidence of hemorrhoids is relatively high during pregnancy partly due to the compression of the major vessels in the anorectal area during this condition. No studies on the use of the anorectal drugs in pregnant women were found. However, the Panel considered several basic factors for formulating a recommendation for the use of anorectal drugs in pregnant women: (1) Because of the extreme complexity of the subject of teratogenesis (Refs. 1 and 2), drug effects on the fetus (Refs. 3 and 4), and the difficulty in demonstrating these effects, coupled with the emerging information that a number of drugs, i.e., thalidomide, certain anticonvulsants, and tetracycline do appear to have these effects, it has been generally accepted that only essential drugs be used in the pregnant woman or the nursing mother.

(2) The major concern regarding the use of anorectal drugs in this group relates to the potential for systemic absorption and thus fetal exposure or exposure of the newborn with its immature protective systems. Although data are lacking, the Panel has concluded that systemic absorption of drugs is usually of significant concern only when agents are applied intrarectally. Therefore, concern relates only to those agents available for intrarectal use.

(3) The only drugs used intrarectally of concern are those which have a

potential for being absorbed through mucous membranes. Anorectal agents designated as Category I protectants that have no other pharmacologic activity are, as a class (e.g., petrolatum), generally not absorbed significantly, and thus would be acceptable.

On the basis of these considerations, the Panel makes the following recommendations regarding the use of anorectal products in pregnant and nursing women:

(1) Any ingredient that is in Category I for external anorectal use may be used by pregnant and nursing women.

(2) Any ingredient that is a Category I protectant that has no additional pharmacologic effect may be used intrarectally by pregnant and nursing women.

(3) All intrarectal ingredients, except those Category I protectants that have no additional pharmacologic effect, must carry a warning: "The safety of this product has not been established for use by pregnant women or by nursing mothers," (See part II. paragraph Q.5. below—Warnings.)

References

(1) Meester, W. D., "The Effects on the Fetus of Drugs Given During Pregnancy," *Marquette Medical Review*, 30:147–154, 1964.

(2) Tuchmann–Duplessis, H., "Embryonic Clinical Pharmacology," *in* "Drug Treatment. Principles of Practice of Clinical Pharmacology and Therapeutics," Edited by Avery, G. S., Publishing Sciences Group, Inc., Actin, MA, pp. 44–56, 1976.

(3) Singh, S. and B. L. Mirkin, "Fetal Clinical Pharmacology," *in* "Drug Treatment. Principles of Practice of Clinical Pharmacology and Therapeutics," Edited by Avery, G. S., Publishing Sciences Group, Inc., Actin, MA, pp. 57–70, 1976.

(4) Boreus, L. O., "Fetal Pharmacology," Raven Press, New York, 1973.

O. Pediatric Dosage

The Panel concludes that the safety of protectants and astringents would not preclude their use in the pediatric age group between 2 and 12 years at the same dose level as approved for adults. However, the Panel has concluded that studies of all other anorectal drugs, in the pediatric age group are negligible or non-existent. Therefore, anorectal drugs other than protectants and astringents should not be used in children under 12 years of age, except on advice of a physician, until studies are done to show safety and effectiveness at specific dose levels for children according to measurable parameters such as body weight.

The Panel is also aware that pediatric patients do not comprise a substantial proportion of the patients who receive these OTC products. Chronic constipation, fecal impaction, and straining on elimination of the stool do not lead to hemorrhoids in children nearly as frequently as they do in adults (Ref. 1). Although anal fissures and rectal prolapse are not uncommon, hemorrhoids are, on the other hand, less common in infants and children (Ref. 1).

Frequently, children are diagnosed by their parents and perhaps by physicians to have hemorrhoids when in fact the symptoms may be due to conditions such as rectal prolapse, parasitic conditions, and a variety of congenital disorders such as cystic fibrosis and megacolon (Refs. 2 and 3). Hemorrhoids, when seen in children, may be due to some underlying and often serious cause such as vena caval or mesenteric obstruction, cirrhosis, portal hypertension associated with liver disease, or other causes resulting in venous obstruction (Refs. 1 and 2). Hemorrhoids in children usually subside without surgery when the primary condition is corrected (Ref. 1). However, OTC anorectal preparations have been used on occasion for symptomatic relief (Refs. 1, 2, and 3).

The use of anorectal ingredients other than protectants and astringents in children 2 to 12 years is not appropriate in view of the multiplicity of such severe signs and symptoms, except under a doctor's supervision with treatment directed at the primary cause (Ref. 2).

In summary, the Panel concludes that most anorectal disorders in children are brought to a physician for evaluation and treatment. Thus, there is no target population in children for OTC anorectal products that contain other than protectants and/or astringents. (See part II. paragraph Q.5 below—Warnings.)

References

(1) Letter to DeCillis, T. D. from J. M. Arena is included in OTC Volume 120051.

(2) Letter to DeCillis, T. D. from H.F. Eichenwald is included in OTC Volume 120051.

(3) Letter to DeCillis, T. D. from C. R. Angle is included in OTC Volume 120051.

P. Inactive Ingredients

A variety of inactive ingredients (pharmaceutic necessities) are used in the manufacture and formulation of anorectal products. These inactive ingredients are intended for a variety of purposes such as aromatics, vehicles, or colorants.

For various reasons, individuals may wish or need to avoid using certain inactive ingredients found in OTC drug products. These reasons may include allergic reactions, idiosyncratic responses, fear of safety (whether valid or not), or personal dislike. It is impossible to make a free choice in this regard unless the full contents of drug products are listed in the labeling. The Panel is aware that the Federal Food, Drug, and Cosmetic Act does not require the labeling of inactive ingredients if none of the inactive ingredients are identified in the general conditions for use and labeling of inactive ingredients as published in the **Federal Register** of April 12, 1977 (42 FR 19156). This notice also indicates that if one inactive ingredient is identified, all such ingredients must be identified in type size one-half of that used for active ingredients. However, for the reasons noted above, this Panel strongly recommends full ingredient labeling of inactive as well as active ingredients for all drug products. (See part II. paragraph Q. below—Labeling.) In support of this position the Panel notes that labeling and composition regulations for food and food products, as published in the **Federal Register** of October 19, 1976 (41 FR 46156), and cosmetics labeling in accordance with Part 701 (21 CFR Part 701) are already requiring such labeling. Because the purpose of an OTC drug is to alleviate symptoms, it would seem much more compelling to have inactive ingredient information on all OTC drugs. The Panel reaffirms the FDA proposal on inactive ingredients, as published in the **Federal Register** of April 12, 1977 (42 FR 19156), that marketed products should contain only those ingredients essential to the product. Therefore, the Panel concludes that the consumer should be exposed to the least number of ingredients possible.

The Panel recognizes that several inactive ingredients may be required for the formulation of products and that certain of these inactive ingredients may affect the safety and effectiveness of an active ingredient. (See part II. paragraph G. above—Bioavailability of Anorectal Dosage Forms.) In addition, certain ingredients may serve both functions, i.e., as an active and as an inactive ingredient; petrolatum, for example, can act as a protectant or as a vehicle for active ingredients. Perfumes are known sensitizing agents and the risk of adverse reactions increases with each perfume present.

The Panel concludes that pharmaceutical necessities should be included in the labeling. When perfumes are included in anorectal products, the following warning is required: "If redness, burning, itching, swelling, pain, or other symptoms develop or increase, discontinue use and consult a physician." (See Part II. paragraph Q.2.d. below—Warning for anorectal products containing perfume.)

The Panel has reviewed the available literature and submitted data regarding the safety of many of the inactive ingredients contained in anorectal preparations. It is the view of the Panel, however, that the final decisions concerning and the safety and advisability of including these inactive ingredients in drug products be reviewed by an appropriate body. Because many of these ingredients are used in the formulation of many drug products, it is not appropriate that they be dealt with specifically and solely in relation to anorectal products.

The Panel has reviewed the inactive ingredients present in the data submitted to the Panel and complete statements on certain inactive ingredients were prepared which have been appended to the Panel's minutes and are available from the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

The Panel wishes to alert those interested individuals of the Panel's concerns regarding the safety of the following inactive ingredients: Eucalyptus oil, sodium lauryl sulfate, tyloxapol, benzyl benzoate, and perfumes. There are data to suggest that the safety of these ingredients especially merit further study by an appropriate review panel.

Q. Labeling

1. *General comment.* The panel has established three distinct types of labeling for anorectal ingredients, i.e., general labeling, labeling for each pharmacologic group, and individual active ingredient labeling. The labeling discussed in this section is of a general nature and is applicable to the anorectal active ingredients in all pharmacologic groups discussed within this document. The Panel has also recommended specific labeling for each pharmacologic group of ingredients, and that labeling is applicable to each ingredient within that pharmacologic group. Furthermore, in some cases, the Panel has recommended specific labeling for an individual active ingredient and such labeling is applicable only to that ingredient.

Terms such as "greaseless," "stainless," and "vanishing" are intended to provide useful information to the consumer. However, the Panel concludes that such terms are descriptive and not indications for use. These terms must clearly be separated from drug claims made in labeling.

The Panel has accepted the OTC drug review labeling standard as set forth in 21 CFR 330.10(a)(4)(v) which requires that:

> Labeling shall be clear and truthful in all respects and may not be false or misleading in any particular. It shall state the intended uses and results of the product; adequate directions for proper use; and warnings against unsafe use, side effects, and adverse reactions in such terms as to render them likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

The Panel concurs with the above labeling requirement as well as the following statement of identity as set forth in 21 CFR 201.61(b):

> Such statement of identity shall be in terms of the established name of the drug, if any there be, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. In the case of an over-the-counter drug that is a mixture and that has no established name, this requirement shall be deemed to be satisfied by a prominent and conspicuous statement of the general pharmacological action(s) of the mixture or of its principal intended action(s) in terms that are meaningful to the layman. * * *

In most cases, the pharmacologic activity of the ingredients reviewed in this document has been demonstrated in body sites other than the anorectal area. However, OTC anorectal ingredients may share a common action in that they relieve the symptoms of pain, itching, burning, and/or swelling, but the pharmacologic activity of many of these active ingredients has not been proved in the anorectal area. It is the opinion of the Panel that consumers will be unable to understand labeling that identifies an anorectal product only by its pharmacologic activity, e.g., local anesthesia. However, they could readily understand an anorectal product that is labeled for its intended use and will provide symptomatic relief. For example, the consumer can understand labeling that says an anorectal product will relieve pain, burning, and itching better than labeling that would identify the anorectal product as a local anesthetic.

For this reason, the Panel has concluded that anorectal ingredients and combinations shall be labeled in terms of the intended use of the product, that is, for the relief of anorectal symptoms such as pain, burning, and itching. Further, the Panel concludes that all ingredients and combinations of such ingredients considered within this document shall be designated as "anorectal agents" or "anorectal products" to reflect the intended use of the ingredient or combination of such ingredients so that consumers will know exactly the intended use of the product. Anorectal agents may include any Category I active ingredient for the relief of symptoms, such as pain, burning, itch, or swelling, which are identified in this document by their usual, respective pharmacologic classifications, e.g., local anesthetics, vasoconstrictors, protectants, counterirritants, keratolytics, and astringents. The Panel has used the traditional pharmacologic classifications only to establish a logical grouping of the ingredients for discussion in this document but has placed the use of specific pharmacologic classifications as labeling claims in Category III until such pharmacologic activity can be proven in the anorectal area. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.) If such pharmacologic activity can be proven in the anorectal area, the product can also be identified by its specific pharmacological activity, but this does not exclude the requirement for product designation as an anorectal agent or anorectal product.

2. *General principles and recommendation.* In addition to the specific labeling recommendations listed in the individual ingredient statements contained within this document, the Panel concludes that the following general principles and recommendations also apply for truthful and accurate labeling:

a. *Labeling of anorectal products.* The labeling of every marketed anorectal product shall be clearly designated as an "anorectal" product to reflect the product's intended use, in addition to a statement of indication such as, "For the temporary relief of discomfort associated with hemorrhoids and other anorectal disorders." (See part II. paragraph Q.4. below—Indications.)

When the product is intended for use on concurrent symptoms, the symptoms must be specified.

b. *Quantitative active and inactive ingredient listing.* The Panel is aware that current regulation only requires the listing of active ingredients and does not require quantitative or inactive ingredient labeling. However, the Panel recommends the following: (1) A quantitative listing of each active ingredient in an anorectal product should be indicated in the labeling. The concentration of each active ingredient should be given per suppository, applicatorful, or other unit of dose.

(2) All inactive ingredients in an anorectal product should be listed in the labeling by their established names and adhere to the proposed inactive ingredient regulation as published in the **Federal Register** of April 12, 1977 (42 FR 19156).

c. *Directions for use for all anorectal products.* The labeling of all anorectal products must contain the following information as indicated under the heading "Directions for use": Recommended or usual dosage, frequency of administration (e.g., every 4 hours, three times daily), and site of administration (i.e., external or intrarectal application).

Panel members have continually emphasized the importance of anal hygiene. This is essential in achieving symptomatic improvement of anorectal disorders; therefore, the Panel recommends the inclusion of the following directions for use on the labeling of all anorectal products, "When practical, wash the anorectal area with mild soap and warm water and rinse off all soap before application of this product."

d. *Warning for anorectal products containing perfume.* When perfume is included in anorectal products, the following warning is required: "If redness, burning, itching, swelling, pain, or other symptoms develop or increase, discontinue use and consult a physician." (See part II. paragraph P. above—Inactive Ingredients.)

3. *Directions for use for specific anorectal dosage forms.* The Panel also recommends the following specific labeling for the various anorectal dosage forms, as indicated for specific anorectal products under the heading "Directions for Use."

a. *External Use*—(1) *For products that are ointments, pastes, creams, jellies, foams, or gels.* "Apply externally to the anorectal area."

(2) *For products that are pads containing anorectal ingredients.* "Gently apply by patting and then discard."

(3) *For products that are ointments, pastes, creams, jellies, foams, pads, or gels for external use only.* "For external use only."

b. *Intrarectal use*—(1) *For products that are wrapped suppositories for insertion into the rectum.* "Remove wrapper before inserting into the rectum."

(2) *For all products to be inserted into the rectum.* "For use by insertion into the rectum."

(3) *For products that are to be used with special applicators such as pile pipes or other mechanical devices.* "Gently insert applicator into the rectum."

c. *External and intrarectal use.* Many anorectal products may be used externally as well as intrarectally. Whenever a manufacturer markets a product for both external and intrarectal use, the following labeling must appear on the product and clearly separate each set of directions under the headings, "For external use" and "For intrarectal use":

(1) *For external use—For products that are ointments, pastes, creams, jellies, foams, or gels.* "Apply externally to the anorectal area."

(2) *"For intrarectal use*—(i) *For products that are to be used with special applicators such as pile pipes or other mechanical devices.* "Gently insert applicator into the rectum."

(ii) *For all products to be inserted into the rectum.* "For use by inertion into the rectum."

4. *Indications.* The Panel accepts the following indications as general labeling for anorectal products in addition to specific labeling appropriate for specific ingredients, as discussed later in this document.

a. "For the temporary relief of the discomfort associated with hemorrhoids and other anorectal disorders."

b. "For the temporary relief of itching associated with hemorrhoids and other anorectal disorders."

c. "For the temporary relief of anorectal itching."

d. "For the temporary relief of local itching associated with inflamed hemorrhoidal tissues."

e. "For the temporary relief from the itching and discomfort associated with hemorrhoids and other anorectal disorders."

f. "For the temporary relief of the discomforts associated with piles (hemorrhoids) and other anorectal disorders."

g. "For the temporary relief of symptoms of anorectal disorders."

h. "Gives temporary relief of anorectal itching."

i. "Temporary relief of itching discomfort associated with hemorrhoids and other anorectal disorders."

j. "For the temporary relief of symptoms associated with hemorrhoids and other anorectal disorders."

k. "To temporarily soothe local discomfort associated with hemorrhoids and other anorectal disorders."

1. "To help relieve the discomfort associated with hemorrhoids and other anorectal disorders."

m. "For the temporary relief of itching."

n. "For the temporary relief of symptoms of inflammation associated with hemorrhoidal tissues."

o. "Gives temporary relief due to external hemorrhoids and other anorectal disorders."

p. "For the temporary relief of pruritus ani."

5. *Warnings.* The Panel is aware that some of the recommendations discussed in this section are not required under the current OTC regulations. However, the Panel wishes to make the following statement: Warning statements may be combined to eliminate the duplication of words or phrases, but the combined warning statement must be clear and understandable with no decrease in meaning and emphasis. Warning statements must be included on the container and the package in a "box border"; they should be printed in black ink or in the color of the most prominent type appearing on either the container or the package, that is, in such a fashion that the prominence and meaning of the warning is not obscured. Appropriate use of printing techniques, styles, colors and illustration should be utilized to aid the consumer in encountering and understanding the important meaning of the labeling. Warning or caution statements should be typeset in no less than eight-point type, or one-third the point size of the largest type face appearing on both the container and labeling, whichever is larger.

The Panel concludes that it is irrational and unsafe to recommend that any anorectal preparation be used "as needed" or "by continual application" or "for prolonged use" because this philosophy would promote unrestricted use beyond safe limits for OTC anorectal products. Because these ingredients are to be used on a short-term basis only, i.e., for not more than 7 days without improvement, the Panel considers these directions inappropriate and contrary to the concept of safe and effective ingredients for temporary relief of anorectal symptoms. If symptoms continue to occur or increase, the consumer should consult a physician to avoid any delay in establishing an accurate diagnosis and to begin necessary treatment of any serious disease condition. Furthermore, the continued use of certain ingredients may be harmful by producing an allergic reaction or skin irritation. (See part II. paragraph J. above—Allergy and Sensitization of the Anorectal Area.) Repeated use of anorectal products, while temporarily relieving symptoms, may mask more serious signs and symptoms.

In light of the above discussion regarding continued use, the Panel concludes that the use of anorectal products for more than 7 days is not recommended except under medical supervision and that the following warnings must appear in all labeling of anoretcal products under the heading "Warnings": (1) "If symptons do not improve, do not use this product for more than 7 days and consult a

physician." (2) "Do not exceed the recommended daily dosage except under the advice and supervision of a physician." (3) "If itching persists for more than 7 days, consult a physician." (See part II. paragraph E.1. above—Itching.)

The Panel emphasizes that OTC products are not appropriate for alleviating bleeding that may occur in the anorectal area and strongly recommends the following warning: "In case of bleeding, consult a physician promptly."

The Panel also recommends the following specific labeling be applied to the various anorectal dosage forms when indicated as external and/or intrarectal products under the heading "Warnings":

a. *External use*—(1) *For products that are ointments, creams, jellies, foams, pads, or gels for external use only.* "Do not put this product into the rectum by using fingers or any mechanical device or applicator." (See part II. paragraph B. above—Anatomy of the Anorectal Area.)

b. *Intrarectal use*—(1) *For all anorectal products for intrarectal use by insertion into the rectum, except protectants.* "The safety of this product has not been established for use by pregnant women or by nursing mothers." (See part II. paragraph N. above—The Use of Anorectal Drugs During Pregnancy and by Nursing Mothers.)

(2) *For products that are to be used with special applicators such as pile pipes or other mechanical devices.* "Do not use this product if the introduction into the rectum causes additional pain. Consult a physician promptly." (See part II. paragraph I.2. above—Ointment, creams, gels, jellies, and pastes.)

c. *For all (see outlines) anorectal products that contain at least one Category I anorectal ingredient other than a Category I protectant or astringent active ingredient.* "Do not use this product in children under 12 years of age except under the advice and supervision of a physician." (See part II. paragraph O. above—Pediatric Dosage.).

6. *Drug interaction precautions.* The Panel concludes that it is important for consumers to be aware that certain types of products should not be used concurrently. In such cases, the labeling of anorectal products must contain an appropriate drug interaction precaution under the heading "Drug Interaction Precaution." This warning is not applicable to all anorectal products and is discussed and applied later in this document. (See part III. below—Local Anesthetics and part IV. below—Vasoconstrictors.)

7. *Category II labeling.* The Panel has reviewed the labeling of products and ingredients submitted to the Panel and has concluded that some words and phrases are inappropriate for the OTC marketplace and recommends the withdrawal of these words and phrases from OTC labeling. Of particular concern are labeling claims containing the words "palliative treatment," "for treatment of hemorrhoids," "eliminates," or "treatment." The use of these words only serve to confuse and mislead the consumer because the implication is a curative or definitive action. OTC products are primarily for the relief of symptoms and not the treatment of disease.

Many labeling claims contain words that are too general, unclear, or redundant, and may be misleading when used alone, such as "simple anorectal irritation," "anorectal disorders," "simple inflammatory rectal conditions," "removes common causes of local irritation," "simple," "common," "uncomplicated," "minor," "superficial," "for hemorrhoids," "reliences painful distress," "alleviates irritation of mucous membrances," "use as a hygienic aide to remove the common causes of local irritation," "relieves," "soothes," "cools," "cooling," "minor rectal inflammation and irritation," "simple inflammatory rectal conditions," "in most cases," "concealed hemorrhoidal tissue," and "uncomplicated hemorrhoids."

The Panel is also concerned with the use of words or phrases describing anorectal conditions that are not easily disgnosed by the consumer and therefore are not appropriate for the OTC market, such as "anal eczema" and "psoriasis." Furthermore, the Panel is aware of current labeling that instructs the consumer to use the product "before or after hemorrhoidectomy," "for anorectal surgical wounds," "episiotomies," or ". . . sclerosing therapy." The Panel concludes that such labeling is not appropriate for consumers because these conditions are best treated under the advice and supervision of an attending physician.

The Panel has concluded that the use of certain protectant ingredients can provide lubrication in the anorectal area in the sense of making the area less dry and more pliable. (See part V. below—Protectants.) However, the Panel is aware of current labeling that is misleading because of reference to lubrication in the sense of laxation. The amount of lubricant used in anorectal preparations is not sufficient for laxation. The Panel, therefore, concludes that any wording or phrase that implies laxation, such as "provides lubrication and thus facilitates bowel movements," is clearly inappropriate.

Several products currently on the OTC market make claims of healing. The Panel concludes that such labeling as "natural healing is encouraged" implies a definitive therapeutic action not appropriate for OTC use as well as an implication that other products are synthetic or unnatural.

There are additional labeling claims currently used that state inaccurate or unproven facts. Because there are no sensory pain nerve fibers present in the rectal mucosa, words and phrases such as "temporarily relieves rectal itching" and "temporarily relieves rectal irritation" are clearly inappropriate as there is no feeling of pain or itch in the rectum.

Some labeling may cause the consumer to believe that certain products are superior to other available products for any of a number of reasons, for example: "contains no narcotic, anesthetic or habit forming ingredients," "nonnarcotic," "without the use of narcotics," or "contains no stinging, smarting astringents." These claims clearly imply a stronger or more effective product and also imply greater safety. Furthermore, the labeling implies that other products are narcotics, anesthetics, or astringents and are harmful without any evidence that this is so.

Labeling such as "medicinal," "recommended by physicians," "recommended by doctors," or "doctor tested" is misleading because these terms suggest that other products are not medicine or that other products are of no value because physicians do not recommend the other products or that all physicians recommend these products. If a product has been studied by scientifically approved methods, such information is acceptable as a basis for claims in labeling.

Claims as to length of effectiveness have not been proven and such claims as "sustained," "prolonged," or "effective over a long period of time" are not appropriate.

Claims such as "helps prevent scratching," "quiets the urge to scratch," and "checks scratching" are unproven and, furthermore, it is highly unlikely that prevention of scratching is possible. The desire to scratch occurs in some consumers whether or not itching is present. None of the data submitted refer to scratching as a symptom.

A claim such as "avoids embarrassment" is esthetic rather than a rational drug claim and is not appropriate for the OTC market.

Claims such as "torment" or "relieves the torment of . . ." are strong implications of extreme discomfort and the use of such claims is both excessive and misleading.

Claims such as "deeply penetrates mucous membranes," "penetrates denuded skin surfaces," and "reduces swelling of the mucosa and skin thus permitting a deep penetration of other ingredients" are not accurate. These statements have not yet been proven in the data submitted and are misleading because they imply a deep-seated source of discomfort.

8. *Category III labeling.* The Panel concludes that many labeling claims currently being made for OTC anorectal products have not been fully substantiated by the data presented to the Panel. However, the Panel is of the opinion that further testing is necessary to prove the appropriateness of these claims for Category I status.

The Panel classifies the following claims as Category III:

(1) "Holds the active ingredients in close contact with the irritated skin, thereby prolonging the beneficial action."

(2) "Prompt," "promptly," "fast," "quick," "quickly," "in minutes," and "rapidly" are Category III claims that can move to Category I if an ingredient can be shown to act within 20 minutes after application.

(3) "Prompt relief obtained for (specific number of hours) from pain and itching" and "promptly relieves pain and itching for (specific number of hours)," can be Category I claims if an ingredient can be shown to act within 20 minutes after application and the relief lasts as long as specified.

R. Pharmacologic Classifications of Anorectal Ingredients

Not all anorectal ingredients and products are used for the same indication; therefore, the requirements for effectiveness should not be the same. In an attempt to classify anorectal active ingredients used in the products submitted, it was necessary to distinguish between the pharmacologic activities and the resulting effectiveness for the claims of these products.

The Panel reviewed all anorectal active ingredients submitted to the Panel. The following pharmacologic classification of anorectal ingredients was developed by the Panel in an attempt to simplify categorization of ingredients and thereby eliminate labeling confusion: Local anesthetics, vasoconstrictors, protectants, counterirritants, astringents, wound-healing agents, antiseptics, keratolytics, anticholingerics, miscellaneous anorectal ingredients.

BILLING CODE 4110-03-M

S. Summary Tables of Ingredient Classifications.

1. Category I (E--External Use and I--Intrarectal Use).

Local Anesthetics	Vasoconstrictors	Protectants	Counterirritants	Astringents	Keratolytics
Benzocaine in polyethylene glycol ointment (E).	Ephedrine sulfate in aqueous solution (E, I).	Aluminum hydroxide gel (E, I)	Menthol in aqueous solution (E).	Calamine (E,I)	Alcloxa (E)
					Resorcinol (E)
Pramoxine hydrochloride in a cream formulation (E).	Epinephrine hydrochloride in aqueous solution (E).	Calamine (E, I)		Witch hazel water (E)	
		Cocoa butter (E, I)		Zinc oxide (E,I)	
Pramoxine hydrochloride in a jelly formlation (E).	Phenylephrine hydrochloride in aqueous solution (E, I).	Cod liver oil (E,I)			
		Glycerin in aqueous solution (E).			
		Kaolin (E, I)			
		Lanolin (E, I)			
		Mineral oil (E, I)			
		Shark liver oil (E, I)			
		Starch (E, I)			
		White petrolatum (E, I)			
		Wool alcohols (E, I)			
		Zinc oxide (E, I)			

2. Category II (E--External Use and I--Intrarectal Use).

Local Anesthetics	Vasoconstrictors	Protectants	Counter-irritants	Astringents	Antiseptics	Keratolytics	Anticholinergic	Miscellaneous
Diperodon (E)	Epinephrine hydrochloride (I).	Bismuth subnitrate (E,I).	Camphor (E,I)	Tannic acid (E,I).	Boric acid (E,I).	Precipitated sulfur (I).	Atropine (E,I).	Collinsonia extract (E,I).
Phenacaine hydrochloride (E,I).	Epinephrine undecylenate (I).		Hydrastis (E,I).		Boroglycerin (E,I).	Resorcinol (I).	Belladonna extract (E,I).	E. coli vaccines (E,I).
			Menthol (I)		Hydrastis (E,I).	Sublimed sulfur (l).		Lappa extract (E,I)
			Turpentine oil, rectified (E,I).		Phenol (E,I).			Leptandra extract (E,I).
					Resorcinol (I)			Mullein (E,I).
					Sodium salicylic acid phenolate (E,I).			

3. Category III (E--External Use and I--Intrarectal Use).

Local Anesthetics	Vasoconstrictors	Protectants	Counter-irritants	Wound-healing agents	Antiseptics	Keratolytics
Benzocaine in polyethylene glycol ointment (I).	Epinephrine (E,I)	Bismuth oxide (E,I).	Juniper tar (E,I).	Cod liver oil (E,I)	Resorcinol (E)	Precipitated sulfur (E).
Benzyl alcohol (E,I).	Epinephrine undecylenate (E).	Bismuth subcarbonate (E,I).		Live yeast cell derivative (E,I).		Sublimed sulfur (E).
Dibucaine (E,I).	Phenylephrine hydrochloride suppositories (I).	Bismuth subgallate (E,I).		Peruvian balsam (E,I).		
Dibucaine hydrochloride (E,I).				Shark liver oil (E,I)		
Diperodon (I).				Vitamin A (E,I).		
Dyclonine hydrochloride (E,I).				Vitamin D (E,I).		
Lidocaine (E,I).						
Pramoxine hydrochloride in a cream formulation (I).						
Pramoxine hydrochloride in a jelly formulation (I).						
Tetracaine (E,I).						
Tetracaine hydrochloride (E,I).						

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III. Local Anesthetics

A. *General Discussion*

The Panel defines local anesthetics as agents that produce local disappearance of pain, burning, itching, irritation, and/or discomfort by reversibly blocking nerve conduction when applied to nerve tissue in appropriate concentrations. Any ingredient claimed to be a local anesthetic must act by this mechanism. Theoretically, these effects could be manifested either on perianal skin or mucous membrane.

Local anesthetics, sometimes called topical anesthetics, share several general characteristics: (1) They are capable of acting on all conductive cellular membranes, including nerve tissue, cardiac, smooth, and skeletal muscle to alter conduction of electrical impulses and thus alter function of these tissues; (2) their structure is almost invariably composed of a lipid or fat-soluble portion connected by an intermediate molecular chain of specific lengths to a water-soluble component, usually a secondary or tertiary amine that can exist as a salt or base; (3) they can produce allergic reactions (Refs. 1, 2, and 3).

As anorectal ingredients, local anesthetics are applied both to rectal mucous membranes overlying large veins and to intact and/or abraded skin. The drugs have very different effects on these sites, and these effects are discussed below. Therefore, the Panel has classified ingredients for use at both sites.

1. *Intrarectal use.* The Panel concludes that there is insufficient evidence to prove safety or effectiveness of the local anesthetics used intrarectally (internally) in OTC anorectal products. Local anesthetics can easily diffuse through mucous membranes and, when applied intrarectally, can be absorbed directly into the systemic central and portal blood circulations (Refs. 4 and 5). Under certain conditions this absorption will be almost as rapid as intravenous administration (Refs. 6 and 7). Demonstration of the systemic absorption of an intrarectally administered local anesthetic in an anorectal preparation was presented to the Panel (Ref. 8). Both local and systemic absorption are concommitantly affected by conditions such as pH and formulation (Refs. 9 and 10). (See part II. paragraph G. above—Bioavailability of Anorectal Dosage Forms.) The achievement of a local effect tends to correlate with local absorption if sensory nerves are present; systemic effects also correlate with absorption (Ref. 11). Therefore, those local anesthetics that are the most effective are also the most toxic. Some local anesthetics are potentially toxic when applied to mucous membranes; they are absorbed systemically and in rare cases have caused death (Refs. 4 and 12).

The intrarectal effectiveness of all local anesthetics remains unsubstantiated and requires further testing. The Panel has carefully reviewed all available literature pertaining to this matter and has requested the opinion of several consultants (Refs. 13, 14, and 15). Although a wide variety of products are currently used intrarectally, several factors raise questions as to the therapeutic rationale for this route of administration (Refs. 16 and 17). There are no known sensory pain fibers above the anorectal (dentate) line (i.e., in the rectum). Clinically, one can demonstrate this by the fact that rectal mucosa can be damaged by electric cautery, biopsied, or incised with no pain. However, the sensation of pain in the rectum can be produced by bowel distention due to gas of feces. It has been argued that the mechanoreceptors associated with autonomic afferent fibers mediating this pain may be affected by intrarectal local anesthetics (Refs. 18, and 19 through 26). The use of a local anesthetic would be inappropriate because the signal indicating the need for evacuation would be lost if the local anesthetic were effective. Thus, the use of local anesthetics intrarectally raises a question because, theoretically, constipation might result from anesthesia of distention receptors in the rectal area and could also contribute to the increase of symptoms in the presence of anorectal disease (Refs. 19 through 26).

Another argument for effectiveness of intrarectal local anesthetics is that there is a deposit of local anesthetic along the external anorectal area in the course of introducing the product into the rectum (Ref. 27). This may occur, but the Panel concludes that the primary purpose of intrarectal local anesthetics is the relief of intrarectal symptoms.

A final argument is that medication placed in the rectum will seep out to affect the area below the anorectal line. Although seepage sometimes occurs in anorectal disease, the Panel concludes that this is a symptom that requires the attention of a physician and is not justification for using local anesthetics.

Two studies have been presented to the Panel which have examined the question of clinical pain relief with intrarectal use of two different local anesthetics. One well-designed, double-blind crossover study failed to demonstrate a significant difference between a placebo and a marketed ointment containing a local anesthetic (Ref. 28). Another study demonstrated no significant difference between control and local anesthetic products (Ref. 29). Therefore, the Panel concludes that the safety and the rationale for use, and thus the effectiveness of antrarectal local anesthetics in OTC anorectal products, remains to be established.

2. *External use.* Many local anesthetics have little effect on intact skin because of insignificant absorption. However, certain drugs that are alkaline in nature, poorly ionized, and lipophilic can penetrate the intact skin (Ref. 9). In addition, when the protective keratin layer of the skin is absent due to trauma or inflammation, local anesthetics in proper concentrations are effective on direct contact. Although local anesthetics can be absorbed to some extent, systemic absorption is not as rapid or as great from abraded skin as it is from mucous membranes. Therefore, the potential absorption from perianal skin does not constitute a significant hazard. Because the majority of anorectal disorders are associated with inflamed or denuded skin, the Panel concludes that, under the conditions set forth later in this document relating to concentration, pH, and formulation, certain OTC products containing local anesthetics are effective to relieve pain, itching and burning, irritation, and/or discomfort in this area. Ingredients approved for external use only should not be inserted into the rectum (intrarectally) by any device or in any dosage form.

Due to similarities in chemical structure, all of the local anesthetics are potentially capable of producing significant allergic reactions, both locally and systemically (Refs. 30, 31, and 32). A major consideration is that symptoms of allergy in the anorectal area such as itching and burning are indistinguishable from the same symptoms due to the anorectal disease. Accordingly, the Panel concludes that the labeling of anorectal products containing local anesthetics should bear the following warning about potential allergenicity, *"Caution:* Certain persons can develop allergic reactions to ingredients in this product. If the sympton being treated does not subside or redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a physician." (See part III. paragraph B.1. below—Category I Labeling.)

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3. *Minority report concerning the intrarectal use of local anesthetics.* The majority of the members of the Panel have concluded that local anesthetics used intrarectally are not proven effective at this time. It is believed that the majority based their conclusion on the fact that there are no anatomically identifiable sensory nerve endings or nerve fibers in the rectal mucosa or submucosa. Sensory nerve endings such as Ruffinian corpuscles, end bulbs of Krause, or Pacinian bodies are not reportedly identifiable in these outer layers of the rectum, above the anorectal line. However, there are known and identifiable nerve fibers and plexuses between the muscular layers that are associated with peristaltic muscular contraction of the rectum. These nerves are part of the autonomic nervous system and most are related to the pudendal plexus. Although the autonomic nervous system is primarily associated with motor function, the minority concludes 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. Visceral afferent fibers from the rectum traverse the pelvic plexus and pass into visceral branches of the second, third, and fourth sacral nerves (Ref. 1).

The Panel heard statements and received reports from consultants regarding rectal innervation. The opinions varied and statements have been unspecific and, at times, have represented conflicting opinions regarding the alleged absence of sensation of the rectum.

The Panel recognizes that local anesthetics can be absorbed across the rectal mucosa and penetrate deep enough to enter the systemic circulation. It is acknowledged that the effects of mucous membrane absorption have been documented in statements by the majority regarding the ingredients reviewed. For example, Krantz and Carr (Ref. 2) state, "as a rule, the rectal dose of most drugs is about double the oral dose."

It is the minority opinion that there is definite sensation present in the rectum. It is true that certain superficial mucosal trauma such as rectal biopsy, fulguration, snaring, coagulation, etc., can occur without any associated sensation of discomfort due to pain. However, during instances when biopsy forceps is used which is not sufficiently sharp to effect a quick, clean cut, a pulling of tissue might occur which can be sensed as a significant discomfort. It is also known that there are definite sensory effects when the peritoneal or outer covering layer of an intestinal viscus is stimulated. Dilatation or distention of a hollow viscus such as the rectum produces significant clinical discomfort believed related to constriction of the involved blood vessels, which results in decreased tissue oxygenation (Ref. 3). Anorectal muscular spasm, involving skeletal and/or smooth muscle, can produce discomfort that might be associated with distention of the distal rectum.

The anatomic area above the anorectal line is a highly sensitive area. Any sensitive area requires the presence of physiologically functioning nerve receptors and fibers. This premise is documented by noting that when the rectum is filled with feces or gas, which raises the intraluminal pressure between 20 to 25 cm of mercury, the desire to empty the rectum is experienced. The receptors within the wall of the rectum are not only able to detect increases in pressure (pressoreceptors) but they can also differentiate whether the increase in pressure is due to feces, liquids, or gas (Ref. 4). The discriminating ability of these sensors is relied upon by individuals who risk flatulating in a public place.

The minority concludes that virtually any foreign body within the lumen of the rectum is definitely sensed by an individual who has an intact and nonpathologic nervous system. The mere introduction and insertion of a finger during a rectal examination commonly produces discomfort not only at the anal opening but also within the

luminal wall of the distal rectum. There is no question that such an examination probably also stimulates sensory nerve endings in the perianal skin. However, the distal portion of an inserted intraluminal object can also be sensed when it is in contact with the rectal mucosa. This, probably, is a result of distention pressure on surrounding tissue or deeper tissue layers that contain nerve fiber endings.

Many gastroenterologists, proctologists, and surgeons who perform sigmoidoscopic or colonoscopic examinations are well aware of the pain experienced during this examination in which there is direct contact between the sigmoidoscope and the rectal mucosa. Patients receiving this examination readily attest to the associated, significant rectal discomfort. This pain is sensed above the anorectal line and is associated with the movement of the distal end or tip of the instrument.

The minority concludes that degrees of anesthesia for significant relief of pain can be achieved with the intrarectal use of local anesthetics when anorectal conditions are associated with significant swelling and concomitant or resultant pressure acts to stimulate the sensory nerve fibers. Nerve plexuses in this area are associated with innumerable branching fibers. These nerves are in the ischiorectal area and probably have some branches to the rectum and other branches traversing inferiorly and supplying the perianal tissues below the anorectal line. Therefore, local anesthetics that may block the impulses of the nerve above the branching junction will afford relief of pain and discomfort to areas of the body inferior to the rectum and in the perianal area.

It is unfortunate that this Panel has been required to make conclusions regarding many of the ingredients associated with OTC hemorrhoidal drugs without appropriate clinical studies in the anorectal area. The minority concludes that the majority of the Panel's conclusions are based on the relatively small amount of poorly controlled published studies.

The marketing records or use experience of the various anorectal products containing local anesthetics for intrarectal use are significant. Advertising might be influential regarding the decision for the initial purchase of a product; however, the minority concludes that repeated sales of a product relate to clinical effectiveness. Consumers would not repurchase a product unless relief of symptoms had been achieved and, therefore, in most instances, ineffective products would not remain on the market.

In addition, the minority conclusion has been based greatly upon personal clinical experience with many patients who have attested to obtaining relief of discomfort associated with anorectal disorders with intrarectal use of local anesthetics.

In summary, the minority concludes that the intrarectal use of local anesthetics in OTC anorectal preparations is safe and effective in the dosages recommended in the ingredient statements within this document. This conclusion does not advocate or endorse the use of any specific product or ingredient.

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B. Categorization of Data

1. *Category I conditions under which local anesthetic ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

The Panel has classified the following local anesthetic active ingredients as generally recognized as safe and effective and not misbranded:

Benzocaine in polyethylene glycol ointment (external use)

Pramoxine hydrochloride in a cream formulation (external use)

Pramoxine hydrochloride in a jelly formulation (external use)

a. *Benzocaine in polyethylene glycol ointment (external use).* The Panel concludes that 5 to 20 percent benzocaine per dosage unit in polyethlyene glycol ointment is safe and effective for external use as a local anesthetic in OTC anorectal preparations up to six times daily and not to exceed 2.4 g per 24 hours. Products approved for external use only should not be inserted into the rectum by any device or in any dosage form. Only benzocaine base is discussed below; the salt form has been shown to be ineffective on intact skin and sunburned (abraded) skin (Ref. 1).

(1) *Description.* The local anesthetic benzocaine (ethyl aminobenzoate) is the ethyl ester of para-aminobenzoic acid. Due to its low solubility the base is poorly absorbed through intact skin; absorption through intact mucous membrane is minimal at recommended dosages (Refs. 1, 2, and 3).

(2) *Safety.* If benzocaine is absorbed systemically, reactions may include methemoglobinemia (Refs. 4 through 9). Three cases have been reported in the literature of systemic absorption in patients who developed methemoglobinemia within 3 hours of ingesting 162.5 to 325 milligrams (mg) benzocaine (Refs. 5 through 9). Nine cases of methemoglobinemia with blood levels in concentrations as high as 52 percent methemoglobin in infants treated with lotions, suppositories, or ointments containing benzocaine have also been reported (Refs. 8 and 9). However, Adriani and Campbell (Ref. 2) have used 20 percent benzocaine as a lubricant for intratracheal catheters nearly 10,000 times without untoward effects.

Furthermore, Adriani and Zepernick (Ref. 3) have reported only one case of methemoglobinemia developing in a patient 30 minutes after use of 20 percent benzocaine ointment on mucous surfaces for endoscopic examination in an estimated 144,000 cases seen over a 12-year period. The Panel, therefore, concludes that absorption leading to systemic effects is rare when applied topically and is not a significant consideration for external use.

The majority of unfavorable local reactions reported are of contact dermatitis or allergic sensitization (Refs. 10 through 15). These reactions are related to topical application of benzocaine. Abscesses and necrosis of skin with subsequent ulceration following treatment of pruritus ani with a 10 percent benzocaine product have been reported, but such reports are not applicable to the 7-day maximum use limit recommended in this document for all OTC anorectal products.

In summary, the Panel concludes that benzocaine is safe for external use in the doses described below, although it may cause adverse reactions in some cases, which will be indicated as labeling warnings.

(3) *Effectiveness.* Studies in guinea pigs, canines, and humans reveal that benzocaine is effective only in the base form. As a salt form, it is ineffective in an acid medium (pH 4 to 6) (Ref. 4). In a study of benzocaine base and salt along with 30 other local anesthetic-containing preparations, experimentally induced

itching, burning, and pain in suburned (abraded) skin were relieved by a 20 percent concentration of benzocaine base. The salt form and lower concentrations (below 5 percent) of the base were ineffective. In the same study, 10 to 15 minutes after application of the 20 percent benzocaine in polyethylene glycol ointment on normal skin, electrical stimulation produced no response (Ref. 1). Adriani and Zepernick (Ref. 3) have shown 20 percent benzocaine ointment to have a short onset (less than 30 seconds). Because duration of effect is directly related to duration of contact, effectiveness may be enhanced by slowing the rate of absorption when used in ointments (Refs. 17 and 18). Adriani and Zepernick (Ref. 3) have reported using benzocaine ointment (20 pecent benzocaine in polyethylene glycol ointment) for lubricating endotracheal catheters, oral and pharyngeal airways, and in laryngoscopic and bronchoscopic examinations in an estimated 144,000 cases with negligible side effects (except for one death which is considered to be an idiosyncratic reaction), and successful transient local anesthesia. The effectiveness of 20 percent benzocaine in polythylene glycol ointment applied externally in the anorectal area has been demonstrated in a study of 39 patients with painful hemorrhoids by Schmitz, Smith and Carberry (Ref. 19). The 20 percent preparation in polyethylene glycol ointment demonstrated relief in all patients compared to 15.4 percent and 38.4 percent failures for 1.0 and 0.5 percent benzocaine ointment, respectively (Ref. 19). Of those studies reporting effective use of benzocaine in anorectal disorders, the majority are anecdotal (Refs. 20, 21, and 22), but there are sufficient valid studies to establish effectiveness.

There is no significant difference in effectiveness between benzocaine in polyethylene glycol ointment U.S.P. and benzocaine in polyethylene glycol ointment used in the above studies (Refs. 1 and 23). The Panel concludes, based on studies in the anorectal area and elsewhere, that 20 percent benzocaine in polyethylene glycol ointment is effective, but it is clear that certain other vehicles are not all equally effective in releasing benzocaine from the final formulation (Refs. 19, 23, and 24).

(4) *Dosage.* Adult external dosage is 5 to 20 percent benzocaine per dosage unit in polyethylene glycol ointment up to six times daily and not to exceed 2.4 g per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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(b.) *Pramoxine hydrochloride in a cream formulation and pramoxine hydrochloride in a jelly formulation (external use).* The Panel concludes that 1 percent pramoxine hydrochloride per dosage unit in a cream or jelly formulation is safe and effective for external use as a local anesthetic in OTC anorectal preparations up to five times daily and not to exceed 100 mg per 24 hours. The pramoxine hydrochloride cream and pramoxine hydrochloride jelly referred to here are described in detail in a submission to the Panel (Ref. 1). Products approved for external use only should not be inserted into the rectum by any device or in any dosage form.

(1) *Description.* Pramoxine hydrochloride is chemically unrelated to the benzoate esters. It is an alkoxyaryl alkamine ether, with a change in the chemical configuration of the secondary amines (Ref. 2).

(2) *Safety.* Vairous animal studies have revealed few toxic effects except in large doses including 38 milliliters per kilogram (mL/kg) intravenously in the rabbit, and 460 mL/kg intraperitoneally in the mouse (Ref. 3). No toxic effects were noted in its clinical use as an aerosol foam (Ref. 4) or in suppositories and certain vehicles (Ref. 5) or in proctological procedures (Refs. 4 and 6). Two studies for potential irritation in humans failed to show evidence of reaction following continuous topical application of 1 percent pramoxine hydrochloride (Ref. 3). Although 1 percent of the patients did report transient burning sensation at the site of application in other clincial studies, 1 percent pramoxine hydrochloride used as a local anesthetic on mucous membranes of the tongue, urethral membrane, and the anorectal area was reported to cause no significant irritation (Ref. 4).

One report of toxicological studies of pramoxine hydrochloride in 10 guiena pigs revealed no sensitization; human sensitization testing using the Draize test revealed that the pramoxine hydrochloride was one-fifth as sensitizing as a comparable local anesthetic of unknown type (Ref. 3). Therefore, it can be concluded that pramoxine hydrochloride is capable of producing sensitization but is less likely to produce a reaction than other common local anesthetics because of its different chemical structure (Ref. 7).

In summary the Panel concludes that 1 percent pramoxine hydrochloride in a cream or jelly formulation is safe for external use (Ref. 1).

(3) *Effectiveness.* Anesthesia of mucous membranes of the palate, lip, and tongue has been demonstrated utilizing a 1 to 2 percent aqueous solution of pramoxine hydrochloride (Refs. 8 and 9), but such a formulation is not considered useful in anorectal products because the ingredient will not remain at site of action. Several clinical studies in the anorectal area using a pramoxine hydrochloride formulation indicate its effectiveness in producing local anesthesia as well as relieving symptoms (Refs. 4, 5, 6, and 10). In one uncontrolled study of posthemorrhoidectomy patients, 93 percent claimed good to excellent results (Ref. 4). In another uncontrolled study, all of 67 patients reported improvement. Of 27 patients with uncomplicated hemoorhoids, 18 were found to symptomatically improve sufficiently so as not to require surgery after use of a 1 percent concentration pramoxine hydrochloride formulation for 2 weeks. The remaining 9 of 27 also reported some symptomatic improvement. The remaining 40 patients with anorectal pain were also reported to consistently show symptomatic improvement (Ref. 6). In the same study six patients had a fissure or fistula; five of them could not undergo proctoscopy because of pain, but were able to receive proctoscopy after 1 week of treatment. The improved patients all experienced decreased pain (Ref. 6).

The Panel concludes that pramoxine hydrochloride in a cream or jelly formulation is effective as a local anesthetic in OTC anorectal preparations (Ref. 1).

(4) *Dosage.* Adult external dosage is 1 percent pramoxine hydrochloride per dosage unit in a cream or jelly formulation up to five times daily and not to exceed 100 mg per 24 hours.

(i) *For cream formulation.* Pramoxine hydrochloride 1 percent in a cream base containing methylparaben USP, propylparaben USP, cetyl alcohol NF, synthetic spermaceti NF, sodium lauryl sulfate USP, glycerin USP, and purified water USP.

(ii) *For jelly formulation.* Pramoxine hydrochloride 1 percent in a jelly base containing propylene glycol USP, hydroxypropyl methylcellulose USP (4000 centipoises), and purified water USP.

(5) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

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Category I Labeling

The Panel recommends the following Category I labeling for local anesthetic active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indications.* (1) "For the temporary relief of pain."

(2) "For the temporary relief of itching."

(3) "For the temporary relief of burning."

(4) "For the temporary relief of the discomforts of hemorrhoids (piles) or other anorectal disorders."

(5) "For the temporary relief of itching, burning and soreness of hemorrhoids or other anorectal disorders."

(6) "For the temporary relief of pain and itching of hemorrhoidal tissue or other anorectal disorders."

(7) "For the temporary relief of itching, burning and pain associated with hemorrhoids or other anorectal disorders."

(8) "For the temporary symptomatic relief of pain, itch, burning and soreness of some types of hemorrhoids or other anorectal disorders."

(9) "For the temporary relief of pain and itching due to painful hemorrhoids or other anorectal disorders."

(10) "For the temporary relief of pain and itching of hemorrhoids and other anorectal disorders."

(11) "Temporarily helps numb pain associated with hemorrhoids."

b. *Warnings.* (1) *"Caution:* Certain persons can develop allergic reactions to ingredients in this product. If the symptom being treated does not subside or redness, irritation, swelling, pain or other symptoms develop or increase, discontinue use and consult a physician."

(2) *"Caution:* This product is for external use only. Do not apply inside the rectum in any way."

2. *Category II conditions under which local anesthetic ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal products effective 6 months after the date of publication of the final monograph in the **Federal Register**.

Category II Active Ingredients

The Panel has classified the following local anesthetic active ingredients as not generally recognized as safe and effective or as misbranded:

Diperodon (external use)

Phenacaine hydrochloride (external and intrarectal use)

a. *Diperodon (external use).* The Panel concludes that diperodon is safe at the concentration used in OTC drug products but is not effective for external use as a local anesthetic.

(1) *Description.* Diperodon is a local anesthetic which is structurally different from many other common local anesthetics (Ref. 1). "Assuming that nupercaine is 20 times as active as cocaine, it is then about 8 times as active as diothane, although it is at least 20 times as toxic" (Ref. 2).

(2) *Safety.* There are little data on the safety of diperodon but its safety relates in part to the site of application and use in the marketplace with an approved new drug application since 1939 without significant hazard (Ref. 3).

There are not studies directly relating to the safe external use of diperodon. Although it may be absorbed through abraded skin, the Panel has considered this to be insignificant with regard to systemic toxicity due to the limited area involved.

Local irritation and allergic reaction are possible; however, in the limited reports available, local reactions have not been reported (Refs. 2, 4, and 5). It is likely, based on a longer duration of action, but not demonstrated, that diperodon can cause allergic reactions. Therefore, a general warning should be noted on the label. Diperodon-containing products were involved in only three incidents of accidental poisoning in 1973 and no reports in 1974, but no reactions were reported with them (Refs. 6 and 7).

(3) *Effectiveness.* Diperodon and oxyquinoline benzoate topical ointment was reviewed by the National Academy of Sciences, National Research Council (NAS/NRC) Drug Efficacy Study Group and was classified as possibly effective for the temporary relief of anorectal pain and itching and providing anesthetic and mild antiseptic action as published in the **Federal Register** of June 18, 1971 (36 FR 11756). The marketed product reviewed by the NAS/NRC group was the same product submitted to this Panel.

Diperodon has been used in a 0.5 to 1.0 percent concentration in clinical and experimental circumstances (Refs. 1, 8, and 9). In an effectiveness study, it was compared with benzocaine and lidocaine in eye abrasions and three types of burns on guinea pig skin (Ref. 1).

This study demonstrated variable effectiveness of all three agents depending on site of application and injury, although diperodon did appear to be effective (Ref. 1). An unpublished study showed significantly greater relief of moderate and severe but not mild post-hemorrhoidectomy pain with diperodon than the placebo at 40 and 60 minute intervals (Ref. 10). Other studies showed no statistically significant difference between diperodon and the placebo for pain, pruritus, or burning (Refs. 5 and 11 through 14). A double-blind controlled study showed a trend in favor of diperodon over the placebo but no significant differences (Ref. 15). The Panel concludes that, because of the studies cited above, the effectiveness of diperodon when used externally for anorectal use in concentrations of 0.5 to 1.0 percent has not been established.

(4) *Evaluation.* The studies cited utilize double-blind, controlled techniques in the anorectal area, and the predominant results show no statistical difference between diperodon and placebo. Therefore, it is the conclusion of the Panel that diperodon in anorectal OTC preparations is not effective for external use.

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b. *Phenacaine hydrochloride (external and intrarectal use).* The Panel concludes that phenacaine hydrochloride is not safe because it is readily absorbed and is toxic at the concentrations used in OTC anorectal products. The Panel further concludes that there is insufficient evidence to prove it is effective in anorectal products.

(1) *Description.* Phenacaine hydrochloride is a derivative of phenitidin and was one of the first local anesthetics to be used. Its development was based on the known antineuralgic effects of phenitidin (Ref. 1). It is relatively soluble in water, ethanol, and carbon tetrachloride, but not ether. It is not an ester and differs greatly in chemical structure from the majority of local anesthetics.

(2) *Safety.* Phenacaine hydrochloride is well-absorbed across the mucous membrane and is systemically toxic at specific concentrations (Ref. 2). Therefore, this agent cannot be considered as a safe local anesthetic for OTC use because the dose required to be effective would produce toxic systemic effects. Phenacaine hydrochloride is a more potent and more toxic local anesthetic than cocaine which has well-established toxicity and is effective when used in medical procedures (Ref. 3). No specific data exist related to the safety of phenacaine hydrochloride in anorectal preparations or in other uses requiring application to the mucous membranes. In the eye it has been used in a 1 percent concentration, but absorption is minimal or very small through the sclera, the cornea, and the conjunctiva. Therefore, in 1 percent concentration in the eye no toxic reaction has been recorded (Ref. 2).

Like other local anesthetics, toxicity is related to the effect on the central nervous system and in the heart muscle, including restlessness, tremor, clonic convulsions, and finally, respiratory depression. Phenacaine hydrochloride can also act on heart muscle to cause changes in excitability and conductivity (Ref. 1). In one commercial preparation (Ref. 4), a 20-mg dose per suppository is equal to 40 percent of the maximum allowable dose cited by Dreisbach (Ref. 5). A lower concentration of this agent might render it less hazardous, but because phenacaine hydrochloride has a very short duration of action, even in saturated solutions (Ref. 3), any advantage is reduced by virtue of the frequent applications that are then necessary and that might promote more frequent use, leading to a higher daily dose. At any site at which it is effective, it is also well-absorbed systemically and thus potentially toxic. Phenacaine hydrochloride cannot be considered safe for use in OTC anorectal preparations.

(3) *Effectiveness.* Although there are no available data regarding phenacaine hydrochloride as an anorectal agent, it is a moderately effective local anesthetic with a very short period of action (Ref. 3). One human study of phenacaine hydrochloride's effectiveness shows that 1 percent solutions were capable of eliminating a tingling sensation of the tip of the tongue for 3 minutes and saturated solutions of phenacaine hydrochloride eliminated the tingling sensation for 7.5 minutes (Ref. 3). The Panel concludes that

although phenacaine hydrochloride may be effective, it is unsafe for OTC use.

(4) *Evaluation.* Phenacaine hydrochloride is one of the more toxic of the local anesthetics at effective concentrations and has one of the shortest periods of effectiveness. Phenacaine hydrochloride has been almost completely replaced in the medical armamentarium by many other less toxic, longer acting, and safer local anesthetics. Therefore, it is the conclusion of this Panel that this ingredient cannot be considered safe and effective for OTC anorectal preparations.

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Category II Labeling

The Panel concludes certain labeling claims related to the safety and/or effectiveness of phenacaine hydrochloride are unsupported by scientific data and in some instances by sound theoretical reasoning: (See part II. paragraph Q.7. above—Category II Labeling.)

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the local anesthetic active ingredients listed below. The Panel believes it is reasonable to provide 2 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed in OTC products:

Benzocaine in polyethylene glycol ointment (intrarectal use)
Benzyl alcohol (external and intrarectal use)
Dibucaine (external and intrarectal use)
Dibucaine hydrochloride (external and intrarectal use)
Diperodon (intrarectal use)
Dyclonine hydrochloride (external and intrarectal use)
Lidocaine (external and intrarectal use)
Pramoxine hydrochloride in a cream formulation (intrarectal use)
Pramoxine hydrochloride in a jelly formulation (intrarectal use)
Tetracaine (external and intrarectal use)
Tetracaine hydrochloride (external and intrarectal use)

a. *Benzocaine in polyethylene glycol ointment (intrarectal use).* The Panel concludes that 5 to 20 percent benzocaine per dosage unit in polyethylene glycol ointment is safe for intrarectal use as a local anesthetic in OTC anorectal preparations but that there is insufficient evidence to prove effectiveness.

(1) *Description.* (See part III. paragraph B.1.a.(1) above—Description.)

(2) *Safety.* (See part III. paragraph B.1.a.(2) above—Safety.)

(3) *Effectiveness.* It is known that the anesthetic effect of benzocaine is related to its contact with a surface and that it is poorly soluble. Adriani et al. (Ref. 1) have reported using 20 percent benzocaine in polyethylene glycol ointment on mucous membranes for lubrication of endotracheal catheters, oral and pharyngeal airways, laryngoscopy and bronchoscopy in an estimated 144,000 cases with negligible side effects and successful transient local anesthesia. The use of benzocaine in these patients was to eliminate gag, cough, or laryngospasm reflexes and not primarily to relieve pain. Because there are no sensory pain nerve fiber endings in the mucosa of the gastrointestinal tract (Refs. 2 and 3), effectiveness is not altered by the fact that suppositories and ointment, once inserted, do not stay in the lower rectum but may drift up the rectum from 4 to 12 cm above the anal sphincter (Ref. 4). Relief of pain with benzocaine used intrarectally has not been established (Ref. 5). Thus, the Panel concludes that there are insufficient data to prove that benzocaine 5 to 20 percent concentration in polyethylene glycol ointment used intrarectally is effective in OTC anorectal products as a local anesthetic. (See part III. paragraph B.1.a.(3) above—Effectiveness.)

(4) *Proposed dosage.* Adult intrarectal dosage is 5 to 20 percent benzocaine per dosage unit in polyethylene glycol ointment up to six times daily and not to exceed 2.4 g per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* The Panel has placed 5 to 20 percent benzocaine in polyethylene glycol ointment for intrarectal use in Category III because effectiveness of its use in seriously questioned by anatomical and physiological knowledge indicating no rationale for effective relief of symptoms. However, the possibility exists that benzocaine and other local anesthetics may be effective in the anorectal area. Satisfactory proof of effectiveness would require controlled clinical studies utilizing benzocaine in polyethylene glycol ointment and placebo intrarectally as described elsewhere within this document. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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(5) OTC Volume 12006.

b. *Benzly alchol (external and intrarectal use).* The Panel concludes that 1 to 4 percent benzly alcohol per dosage unit is safe for external and intrarectal use as a local anesthetic in OTC anorectal preparations but that there is insufficient evidence to prove effectiveness.

(1) *Description* This is a simple organic compound found naturally in jasmine, hyacinth, and balsams of Peru and tolu. The synthetic form derived by hydrolysis of benzyl chloride from benzylaldehyde (Ref. 2). This drug is converted by the body to hippuric acid and excreted in the urine (Refs. 1, 3, 4, and 5).

(2) *Safety.* When injected, subcutaneously or intravenously, it can cause irritation and local neurolysis (Refs. 4 and 6). Injection into the blood stream can cause vasodilation; in concentrated solutions, it can cause central nervous system irritation with convulsions and subsequent paralysis of respiratory centers (Refs. 3 and 4). Excessive and repeated contact with the

skin can lead to dermatitis by dehydration and removal of the skin's protective layer of lipids (Ref. 6).

Used in concentrations of 1 to 4 percent, this compound is considered to be of low or slight toxicity. As this compound is used in solutions of 1 to 4 percent and in ointments up to 10 percent, its toxicity at this concentration is slight and/or low because it is not absorbed through the skin or mucous membranes (Refs. 1 and 7). Direct absorption into the blood stream is possible but unlikely, which may be an important factor when used on mucous membranes (Ref. 5).

In summary, the Panel concludes that benzyl alcohol is safe for external and intrarectal use because of poor absorption through skin in the doses described below, although it may cause adverse reactions in some cases which will be indicated as labeling warnings.

(3) *Effectiveness (external use).* Used as a local anesthetic on intact skin it is of little potency. One clinical study claims onset of action in 5 to 7 minutes and duration up to 4.6 hours (Ref. 8). Yet other partially controlled and uncontrolled studies indicate maximum effect for a brief time (Refs. 1 and 3). Claims of long duration of effect are not supported, but relief of itching for short periods of time is suggested by the literature (Refs. 1 and 3). One study showed no penetration through intact skin by 4 percent concentration even when combined with 2 percent benzocaine (Ref. 9).

The Panel concludes that there are insufficient data to conclude that benzyl alcohol used externally is effective in treating the symptoms of anorectal disorders. The compound is only weakly active, and its duration of activity is too short to offer substantial relief.

(4) *Effectiveness (intrarectal use).* Benzyl alcohol is relatively low in potency as compared with other local anesthetics (Ref. 10). On mucous membranes, it is slightly more effective than on intact skin (Refs. 4 and 11). But, even on mucous membranes, duration of effect in controlled studies is one-half hour (Refs. 1 and 3). In addition, benzyl alcohol acts to relieve itching (Refs. 1, 2, and 3). Because rectal mucosa does not itch and, in fact, does not have cutaneous nerve endings (Ref. 12), the validity of using this substance for intrarectal use is questionable. Thus, the Panel concludes that there is insufficient evidence to prove that benzyl alcohol used intrarectally as a local anesthetic is effective in OTC anorectal preparations.

(5) *Proposed dosage.* Adult external and intrarectal dosage is 1 to 4 percent benzyl alcohol per dosage unit up to six times daily and not to exceed 480 mg per 24 hours.

(6) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(7) *Evaluation.* The Panel raises a question concerning the intrarectal effectiveness of benzyl alcohol on an area that does not have sensory nerve fiber endings. At best, this is a short acting, low potency local anesthetic. To prove that benzyl alcohol is effective externally and intrarectally, double-blind, controlled, clinical studies must show statistically significant improvement with benzyl alcohol in final formulation, specifying vehicle, as tested against control, by use of questionnaires. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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c. *Dibucaine and dibucaine hydrochloride (external and intrarectal use).* The Panel concludes that there are insufficient data to prove that 2.5 to 20 mg dibucaine or dibucaine hydrochloride per dosage unit are safe and effective for external or intrarectal use as a local anesthetic in OTC anorectal preparations.

(1) *Description.* Dibucaine is the amide of *N*-diethylethylene-diamine and 2-butoxy cinchoninic acid. The aromatic residue and the terminal diethylamino group are thus joined via an amide linkage, rather than an ester, as is procaine. As a base, dibucaine is slightly water soluble and moderately lipid soluble, but its commonly used salt, the hydrochloride, is soluble in both water and organic solvents (Ref. 1). For the purpose of this discussion, dibucaine and dibucaine hydrochloride are pharmacologically equivalent and will be discussed as dibucaine. These compounds have had wide use as both a spinal and topical anesthetic for many years. Dibucaine and dibucaine hydrochloride are the most potent, toxic, and longest acting of the injectable local anesthetics (Ref. 2).

(2) *Safety (external).* When used externally, dibucaine is likely to be absorbed when applied to abraded or broken skin because of its chemical and physical characteristics, but the extent to which this occurs has not been studied. However, the Panel has concluded that dibucaine used externally in the recommended doses below will not constitute a significant systemic absorption hazard because of the limited area of abraded perianal skin.

The primary safety concern with external use relates to allergic reactions. The anorectal area is covered with clothing and often macerated; it should theoretically be more prone to sensitization. These allergic symptoms can easily be confused with the same anorectal disease symptoms (Ref. 3). Several reports of clinical dermatitis due to dibucaine, some severe, are in the literature (Refs. 3 through 7), and the sensitizing ability of this compound is well-documented (Refs. 8 through 11).

In seven clinical studies reported in a submission to the Panel, approximately 489 patients used a product containing dibucaine for 2 to 28 days under some medical supervision (Ref. 12). There were reports by individuals of more discomfort, vaginal irritation, pruritus, and dizziness after use of a whole 15 g tube (150 mg dibucaine) as one application. Reactions were experienced by 6 of 489 patients for dibucaine as compared with 10 of 279 for control. This study indicates a low rate of adverse

reactions. However, in a recent survey of doctors on the use of a product containing dibucaine, 7.9 percent (435) of the physicians responding reported awareness of adverse reactions to dibucaine, including one report of anaphylaxis and 264 reports of local allergic reactions (4.8 percent) as well as reports of burning (31 reports), pruritis (30 reports), irritation (33 reports), and rash (40 reports) (Ref. 13). The group carrying out the study considered it to be a poorly designed survey. The Panel notes, however, that despite its anecdotal character, the survey would indicate that adverse reactions do occur with the commercial preparation, and published reports do not reflect these occurrences.

Finally, the manufacturer of one preparation has reported 57 cases of local reactions, 20 cases of local irritation, although this represents a very small percentage of reported reactions in comparison to units sold (Ref. 12).

In conclusion, the Panel recognizes the potential for dibucaine to cause local irritation and allergic reactions and the need to indicate this on labeling. However, the Panel also concludes that dibucaine is sufficiently safe for external use in the anorectal area at the recommended dosage.

(3) *Safety (intrarectal use).* The primary concern for safety with intrarectal use of dibucaine relates to the potential for systemic absorption because dibucaine has been shown, along with tetracaine, to have unique cytotoxic effects not seen at any dose with other local anesthetics (Ref. 14). The significance of this potential in the anorectal area has not been established. Local irritation may also need consideration.

Dibucaine appears to have a greater margin of safety than cocaine, which has well-known toxicity. One study compared corneal anesthetic potency to convulsive concentration and found that the ratio for dibucaine was 1:1,500,000 as opposed to 1:33,000 for cocaine (Ref. 15). Thus, dibucaine could be useful at low doses where it might be less toxic.

In comparative studies, dibucaine has been shown to be 15 to 20 times more potent than procaine (Refs. 2 and 15), and an aqueous solution is readily absorbed from mucous membranes and skin (Ref. 16) so that systemic toxicity is possible with the use of anorectal preparations (Ref. 16). The absolute toxic dose in man is not known, although a maximum safe dose of 25 mg has been cited, and recently confirmed by Dreisbach (Refs. 17 and 18). A reasonable estimate of the toxic dose could be made by comparative studies of several local anesthetics administered intravenously in both rabbits (Ref. 19) and humans (Ref. 20), and by recent studies in dogs, monkeys, and humans (Ref. 21).

In both rabbits and humans, the relative toxicity of procaine to tetracaine was found to be approximately 1:8, suggesting comparable models (Refs. 19 and 20). In the rabbit study, the toxicity ratio of tetracaine to dibucaine was 1:0.35. Thus, it could be estimated that each 0.044 mg of dibucaine is equivalent in toxicity to 1 mg procaine when given intravenously in rabbits. In the human study of intravenous tetracaine, approximately 2.5 mg/kg (0.125 mg/minute for 20 minutes) produced central nervous system and cardiac symptoms and/or seizures (Ref. 20). Although no data on intravenous dibucaine use in man were found, the similarity of toxicity ratios of tetracaine and procaine in rabbits and man (Refs. 19 and 20) suggest that toxicity ratios of dibucaine to tetracaine, as established in rabbits, could at least be approximately extrapolated to man. Therefore, a comparable toxic intravenous dose of dibucaine would be approximately 0.8 mg/kg or 56 mg total for a 70 kg person. In the rabbit study (Ref. 19), the lethal dose of tetracaine was 7.4 mg/kg, and for dibucaine 2.9 mg/kg. Further intravenous toxicity estimates are given in another study in which ataxia, muscle tremors, or death were noted in dogs at 3 mg/kg and in monkeys at 0.5 to 1 mg/kg after intravenous doses of dibucaine (Ref. 21). This would tend to corroborate the above estimates.

Finally, data was presented to the Panel relating to the intrarectal absorption of dibucaine (Ref. 21). These studies were carried out on very small numbers of dogs, monkeys, and normal human subjects and measured blood levels of dibucaine after intrarectal administration of a commercial product to all subjects and after intravenous administration in dogs and monkeys. These studies provided relatively consistent estimates of blood levels obtained after administration of the commercially formulated drug. However, the study designs were deficient. Doses were not always comparable between subjects. Position and bowel function of subjects were not controlled. No physiological monitoring of vital signs and electrocardiograms were carried out. The small number of subjects did not allow statistical analysis.

The studies revealed several noteworthy findings: (i) An aqueous solution of dibucaine given intravenously is clearly lethal at levels of 3 mg/kg in dogs and 1 mg/kg in monkeys; (ii) Commercial preparations of dibucaine given intrarectally under the conditions of the study provided measurable blood levels, although these levels were less than 20 percent and usually less than 10 percent of the measured lethal or toxic intravenous doses; (iii) A relatively steady state blood level of dibucaine appears to be obtained within 24 to 48 hours of continuous rectal dosing of approximately three times daily, and there are measurable levels for 48 hours after the last dose.

The investigators concluded that the results suggest that intrarectal absorption of the commercial preparations of dibucaine does not give levels comparable to those seen after intravenous administration and that, because toxic effects were only seen after the higher blood levels were obtained with intravenous use, intrarectal use in man is safe (Ref. 21).

Although it is clear that under the conditions of the study rectal absorption of commercially formulated dibucaine did not give levels conparable to intravenous administration, the Panel has several objections to the study conclusion that intrarectal use of the commercial product is safe in man:(i) Absorption of the intrarectal dibucaine preparation was studied in normal subjects, and blood levels obtained varied two to sixfold in single and multiple doses. The blood levels at the maximum recommended dose of 300 mg daily were not studied (Ref. 22). Furthermore, the maximum safe dose was not established in these studies. In the presence of rectal pathology where the mucosal surface is inflamed or otherwise interrupted, absorption might well be greater and certainly more variable, and expected blood levels can not be estimated on the basis of the study presented (Ref. 21).

(ii) The safety of systemically administered dibucaine has not been studied in man or animals. A study has clearly shown that rectally administered dibucaine is absorbed systemically and has the potential of acting at other sites such as the heart and the central nervous system (Ref. 21). The potential for allergic reaction occurring is increased by the slow rate of elimination of dibucaine. No measures of cardiac or central nervous system function were made in this study, although they obviously would be required.

Reported toxicity causing four deaths in children after ingestion of dibucaine and in one infant after rectal application of an unknown amount of dibucaine, are

significant (Ref. 12); however, these appear to have been accidental overdoses. Nevertheless, these cases indicate potential toxicity from OTC dibucaine products.

No reports of fetal cardiac depression during pregnancy have been found due to dibucaine, but the ease with which this occurs with other local anesthetics (Refs. 23 through 27) would suggest that this is possible with dibucaine as well if it is systemically absorbed after intrarectal use. Limited absorption has been demonstrated and, therefore, suggests a potential safety problem during pregnancy (Ref. 21). The Panel concludes that the use of dibucaine in pregnancy is contraindicated and has recommended an appropriate warning.

Finally, the Panel concludes, on the basis of considerable data studied, that the safety of intrarectal dibucaine remains to be established because of its demonstrated systemic absorption.

(4) *Effectiveness (external use).* Effectiveness of dibucaine is altered by the vehicle and whether the dibucaine is present as the base or the hydrochloride. There were little data on external use. Dibucaine hydrochloride has been shown to be an effective anesthetic lasting 46 minutes after application of 2 to 4 mL of a 0.5 percent aqueous solution (10 to 20 mg) when applied to the tip of the tongue (mucous membrane) (Refs. 28 and 29), but it was not effective when applied to intact or sunburned skin (Ref. 30). Dibucaine base, combined with lanolin, petrolatum, and sodium bisulfite in a commercial preparation, was barely effective on sunburned skin (Ref. 30). In petrolatum, a 1 percent concentration of the base was effective on mucous membranes but not on the intact skin (Ref. 31). Although it is probable that both the base and hydrochloride are effective at low concentrations on mucous membranes and abraded skin, studies of other local anesthetics (Ref. 32) have shown that they are effective when the stratum corneum is interrupted (abraded skin). The conclusions on effectiveness are drawn from studies performed on final formulation (Ref. 30).

A significant proportion of anorectal conditions are characterized by abraded or macerated skin, but there are no studies using dibucaine in the perianal area. Therefore, the Panel has concluded that there are insufficient data to show that dibucaine is effective when used for these conditions.

(5) *Effectiveness (intrarectal use).* Dibucaine as the hydrochloride has been shown to be an effective anesthetic lasting up to 46 minutes after application of 2 to 4 mL of a 0.5 percent aqueous solution (10 to 20 mg) when applied to the tip of the tongue (Refs. 28 and 29). In petrolatum in a 1 percent concentration it was effective on all mucous membranes that are sensitive to pain, but not on intact skin (Ref. 31).

Although the base has been demonstrated to be more effective on skin than the salt, Adriani (Refs. 28, 29, and 33) postulates that this lack of effectiveness may relate to the formulation. It is probable that the hydrochloride is effective at low concentrations on mucous membranes. Thus, dibucaine is probably effective on the abraded or macerated skin of the anorectal area below the anorectal line. Its effectiveness with intrarectal use is less clear. Several clinical studies involving more than 600 patients have not clearly shown the effectiveness of this product for anorectal use (Ref. 34). Two other studies demonstrate that control preparations without dibucaine are quite as effective as the commercial dibucaine preparation (Refs. 35 and 36).

The Panel has considered at length the effectiveness of local anesthetics above the anorectal line (on muccous membrane) and has concluded that, because of the absence of pain sensation in this area, intrarectal local anesthetics are unproven. The results of the study of a dibucaine rectal preparation (Refs. 35 and 36) would tend to support the conclusion of the Panel.

(6) *Proposed dosage.* Adult external and intrarectal dosage is 2.5 to 20 mg per dosage unit up to three to four times daily and not to exceed 80 mg per 24 hours.

(7) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) The following warning is recommended for dibucaine and dibucaine hydrochloride when labeled for intrarectal use: "Not for use in pregnant women because it may cause depression of fetal heart function."

(8) *Evaluation.* The Panel concludes that there is insufficient evidence at this time to recommend dibucaine or dibucaine hydrochloride as safe and effective for external or intrarectal use in OTC anorectal preparations and must be tested. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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d. *Diperodon (intrarectal use).* The Panel concludes that there are insufficient data to provide that 0.5 to 1.0 percent diperodon per dosage unit is safe and effective for intrarectal use as a local anesthetic in OTC anorectal preparations.

(1) *Description.* (See part III, paragraph B.2.a. (1) above—Description.)

(2) *Safety (intrarectal use).* The safety of diperodon for intrarectal use has not been established. As with most local anesthetics, it is likely to pass readily across mucous membranes and thus can be absorbed intrarectally. Toxic levels have not been established, although Dreisbach (Ref. 1) has defined 100 mg or 10 mL of a 1 percent solution of diperodon hydrocholoride as a safe does for topical use. Because it is reported to have a long duration of action, the potential for accumulation may be greater than other local anesthetics (Ref. 2). Diperodon has been shown to cause tissue damage when use for infiltration anesthesia after operations on the anus and rectum (Ref. 3). However, those clinical studies of its use in OTC anorectal drug products have not reported specific adverse effects (Refs. 4, 5, and 6).

(3) *Effectiveness (intrarectal use).* No published studies of the intrarectal use of diperodon have been found.

In an unpublished study with 54 patients with internal and external hemorrhoids, there was no statistically significant difference in effectiveness between drug and placebo for relief of pruritis, burning, or pain (Ref. 4). However, no distinction was made in the results between patients having internal and external hemorrhoids.

In an unpublished study of 50 patients, including patients with internal hemorrhoids, the results indicated only a trend in favor of the active ingredient (Ref. 5). Responses by patients having internal hemorrhoids and those patients using the drug intrarectally for other conditions were not analyzed separately. Therefore, no conclusion relative to intrarectal effectiveness can be reached on these data.

One additional unpublished study with 94 patients receiving an application of ointment on the morning of the first postoperative day resulted in no differences between the drug and the placebo (Ref. 6). The findings do not distinguish between intrarectal and external applications or effectiveness.

(4) *Proposed dosage.* Adult intrarectal dosage is 0.5 to 1.0 percent per dosage unit up to five times daily and not to exceed 100 mg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* The Panel concludes that there is insufficient evidence at this time to recommend diperodon as effective for intrarectal use in OTC anorectal preparations.

Double-blind, well-controlled clinical studies showing statistically significant improvement over control must be performed to prove that diperodon is effective intrarectaly. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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e. *Dyclonine hydrochloride (external and intrarectal use).* The Panel concludes that 0.5 to 1.0 percent dyclonine hydrochloride per dosage unit is safe for intrarectal use as a local anesthetic in OTC anorectal preparations but that there is insufficient evidence to prove effectiveness.

(1) *Description.* A propiophenone derivative, dyclonine is a local anesthetic base that forms salts with hydrochloric acid.

(2) *Safety (external use).* Clinical reports indicate a low incidence of reactions (Refs. 1, 2, and 3). For example, dyclonine in a 1 percent concentration in cream base was applied to 3,656 patients for topical anesthesia; only two cases of proven sensitivity were reported (Ref. 4). Further, 1 percent dyclonine has been used without reported toxic reactions prior to office cystoscopy in more than 1,500 patients (Ref. 1). There are isolated reports of both allergic reactions and cardiovascular collapse (Ref. 4).

In summary, the Panel concludes that dyclonine is safe for external use in the doses described below.

(3) *Safety (intrarectal use).* Toxic levels in humans from anorectal use have not been determined. In a study dealing with the safety of dyclonine hydrochloride following oral administration, 35 patients were given from 300 to 600 mg daily for periods of time varying from 1 to 12 weeks. No undesirable side effects occurred (Ref. 5). Convulsions and cardiovascular effects have been reported in animals by other workers with use of dyclonine (Ref. 4).

Dyclonine has been used effectively in a 1 percent concentration without toxic reactions prior to office cystoscopy in more than 1,500 patients (Ref. 1).

Although the intrarectal safety of dyclonine is unknown, the Panel concludes it to be safe at the recommended dosage in light of its apparent low toxicity at other sites.

(4) *Effectiveness (external use).* In an uncontrolled study, 1 percent dyclonine cream was used on 222 patients, 28 of whom had anogenital pruritus (Ref. 6). Seventeen of the 28 were reported to have "excellent" results in relieving their symptoms. In another uncontrolled study in 26 patients with pruritus ani,

good relief of symptoms was claimed in 19, while 7 of the 26 were considered treatment failures (Ref. 7).

However, in a double-blind study of 1 percent dyclonine cream in patients with various dermatoses, 48 of 58 patients were unable to differentiate between the active preparation and the placebo (Ref. 8).

Dyclonine in a 0.01 percent aqueous solution is effective on the rabbit cornea (Ref. 9) and when applied to the tip of the tongue in humans (Ref. 10).

In summary, dyclonine appears to be a local anesthetic that is active in aqueous solutions on the cornea. However, there are not sufficient clinical studies to substantiate its effectiveness in an anorectal preparation, so its effectiveness as an anorectal agent for external use remains to be established.

(5) *Effectiveness (intrarectal use).* No studies are available that relate to the intrarectal effectiveness of dyclonine. Dyclonine hydrochloride in concentrations of 0.5 to 1.0 percent has a rapid onset of action and a duration of effect comparable to that of procaine when used for topical anesthesia in otolaryngology (Ref. 11). It is absorbed through the skin and mucous membranes (Ref. 11). Although in aqueous solution it is known to be an effective topical anesthetic on mucous membranes (Refs. 8, 9, and 10), its effectiveness in the cream preparation is not well-established (Ref. 4). Further, in view of the absence of pain sensors in the rectum, the Panel has judged that the intrarectal effectiveness of dyclonine remains to be established.

(6) *Proposed dosage.* Adult external and intrarectal dosage is 0.5 to 1.0 percent per dosage unit up to five times daily and not to exceed 100 mg per 24 hours.

(7) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(8) *Evaluation.* The Panel does not have sufficient data at this time to recognize dyclonine hydrochloride as an effective local anesthetic for external or intrarectal use in the treatment of anorectal disorders. The Panel recommends further studies so that dyclonine hydrochloride could move from Category III to Category I. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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f. *Lidocaine (external and intrarectal use).* The Panel concludes that 2 to 5 percent lidocaine per dosage unit is safe for external use, but there is insufficient evidence to prove effectiveness as a local anesthetic in OTC anorectal preparations. Furthermore, there is insufficient evidence to prove safety and effectiveness for intrarectal use in OTC anorectal preparations.

(1) *Description.* Lidocaine is an aminoacylamide. It is a white to slightly yellow crystalline powder that is practically insoluble in water, but very soluble in alcohol and chloroform, freely soluble in ether, and dissolves in various oils and fatty type ointment bases (Refs. 1 and 2).

(2) *Safety (external use).* The Panel concludes that lidocaine is safe for external use in concentrations of 2 to 5 percent. Although lidocaine may be absorbed through abraded skin (Ref. 3), the Panel concludes this to be of insufficient concern due to the limited area involved, as well as the low systemic toxicity of lidocaine.

The local toxicity and allergenicity of lidocaine is lower than that of many local anesthetics, although the potential for allergic reaction does exist (Refs. 4, 5, and 6).

(3) *Safety (intrarectal use).* No information relating to the safety of intrarectal use of lidocaine was found in the literature. Lidocaine enjoys wide use for topical and injection anesthesia as well as intravenously for control of cardiac arrhythmias. When injected, it is considered more potent than procaine (Ref. 7). Chronic administration in controlled experiments in animals in doses far exceeding those in OTC drug products produced no adverse effects (Ref. 8).

The degree of rectal absorption of lidocaine remains unknown, although due to the ease of absorption of local anesthetics across mucous membranes, complete absorption must be presumed (Refs. 9, 10, and 11). However, because lidocaine is used intravenously on a routine basis and the kinetics are well-established (Refs. 12 and 13), the Panel concludes that the dosages proposed for anorectal products would not be a major safety problem.

(4) *Effectiveness (external use).* In concentrations of 2 to 5 pecent, lidocaine in a water-soluble vehicle has been considered effective when applied to mucous membranes and the broken skin (Refs. 1 and 14). Current evidence indicates that lidocaine is ineffective in concentrations of less than 6 percent on unbroken skin (Refs. 3 and 15). Because most anorectal disorders are characterized by abraded (broken) skin, lidocaine is expected to be effective in concentrations of 2 to 5 percent.

Double-blind studies evaluating the effectiveness of a lidocaine ointment versus a placebo in providing temporary relief of pain associated with acute anal fissure seem to indicate lidocaine ointment is effective (Ref. 8). The overall results, however, were inconclusive because both the 5 percent lidocaine ointment and the placebo demonstrated effectiveness, although that of the placebo ointment occurred at a lower level of probability. Further investigation using a larger number of cases of anal fissure than the number reported in the studies is indicated.

Recent data demonstrated the effectiveness of a 2.5 percent lidocaine ointment applied to the back or on the upper arm where the skin was abraded by a strip-tape method or by light curettage (Ref. 16). While the Panel recognizes the effectiveness of lidocaine on other skin sites, the Panel concludes that because of the uniqueness of the anorectal area, effectiveness must be demonstrated in the perianal area.

(5) *Effectiveness (intrarectal use).* The Panel questions the use of a local anesthetic in an area above the anorectal line, i.e., in the rectum where there are no sensory pain nerve fibers, and concludes that there is insufficient evidence at this time to recommend

lidocaine as effective for intrarectal use in OTC anorectal preparations.

(6) *Proposed dosage.* Adult external and intrarectal dosage is 40 to 100 mg per dosage unit up to five times daily and not to exceed 500 mg per 24 hours.

(7) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(8) *Evaluation.* Demonstration of effectiveness may be shown by observations of patients with excoriated skin in the perianal area, or the posthemorrhoidectomy, or postepisiotomy patient, or observations that depend upon artifically induced local abrasions. Demonstrating effectiveness by any one of these methods would satisfy the Panel's requirements regarding the effectiveness of lidocaine for external or intrarectal use in OTC anorectal preparations. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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(16) OTC Volume 120055.

g. *Pramoxine hydrochloride in a cream formulation and pramoxine hydrochloride in a jelly formulation (intrarectal use).* The Panel concludes that 1 percent pramoxine hydrochloride per dosage unit in a cream or jelly formulation is safe for intrarectal use as a local anesthetic in OTC anorectal preparations but there is insufficient evidence to prove effectiveness. The pramoxine hydrochloride cream and pramoxine hydrochloride jelly formulations referred to here are described in detail in a submission to the Panel (Ref. 1).

(1) *Description.* (See part III. paragraph B.1.b.(1) above—Description.)

(2) *Safety.* (See part III. paragraph B.1.b.(2) above—Safety.)

(3) *Effectiveness.* The Panel concludes that 1 percent pramoxine hydrochloride in a cream or jelly formulation (Ref. 1) when used intrarectally has not been shown to be effective as a local anesthetic in OTC anorectal preparations. The data reviewed by the Panel do not provide sufficient evidence of effectiveness (Refs. 2, 3, and 4).

(4) *Proposed dosage.* Adult intrarectal dosage is 1 percent pramoxine hydrochloride per dosage unit in a cream or jelly formulation up to five times daily and not to exceed 100 mg per 24 hours.

(i) *For cream formulation.* Pramoxine hydrochloride 1 percent in a cream base containing methylparaben USP, propylparaben USP, cetyl alcohol NF, synthetic spermaceti NF, sodium lauryl sulfate USP, glycerin USP, and purified water USP.

(ii) *For jelly formulation.* Pramoxine hydrochloride 1 percent in a jelly base containing propylene glycol USP, hydroxypropyl methylcellulose USP (4000 centipoises), and purified water USP.

(5) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* The Panel concludes that there is insufficient evidence at this time to recommend pramoxine hydrochloride in a cream or jelly formulation as effective for intrarectal use in OTC anorectal preparations (Refs. 1 through 4).

To prove that pramozine hydrochloride in a cream or jelly formulation is effective intrarectally, further testing is required. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III ingredients, Combinations, and Labeling in Category I.)

References

(1) OTC Volume 120084.

(2) OTC Volume 120015.

(3) OTC Volume 120039.

(4) OTC Volume 120046.

h. *Tetracaine and tetracaine hydrochloride (external and intrarectal use).* The Panel concludes that 10 to 20 mg tetracaine or tetracaine hydrochloride per dosage unit are probably safe as a local anesthetic in OTC anorectal preparations, but there are insufficient data to prove effectiveness for external or intrarectal use.

(1) *Description.* Tetracaine is a derivative of *p*-aminobenzoic acid in which a butyl group has been substituted for one of the hydrogens of the *p*-amino group (Ref. 1).

(2) *Safety (external use).* Tetracaine is a highly active and toxic local anesthetic (Ref. 2). Although tetracaine potentially can be absorbed through abraded skin, the Panel concludes that sytemic toxicity is not a major concern provided no more than a daily maximum of 100 mg tetracaine is used.

Adriani (Ref. 3) states that allergic reactions are usually the result of repeated exposures or cross-sensitization to drugs of the same or similar classification. Skin sensitivity to tetracaine has been confirmed by patch tests in 24 patients treated topically from 1957 to 1966 (Refs. 4 and 5). Eczema was often severe and cross sensititity was noted on several occasions (Refs. 4 and 5). Many patients are sensitive to tetracaine (Ref. 6), and while sensitivity develops in some patients within 1 or 2 weeks, sensitivity did not occur in others for over a year (Ref. 6). Thus, prolonged use of tetracaine in any of its forms should be undertaken with caution (Refs. 7 through 10). In summary, the Panel concludes that tetracaine is safe for external use in the doses decribed below.

(3) *Safety (intrarectal use).* Absorption from mucous membranes is rapid and may simulate slow intravenous injection (Refs. 2, 3, and 11). Tetracaine has been investigated and it has been found that the LD_{50} (lethal dose for one-half of test animals exposed to a substance) of equally effective concentrations of tetracaine in dogs was

similar to that of intratracheal instillation. Tetracaine is a highly active, highly toxic local anesthetic, about 10 times more toxic than procaine but more active, and can be employed in high dilutions (Ref. 2). Its ability to penetrate mucous membranes far exceeds procaine and approaches that of cocaine (Ref. 12). Tetracaine frequently shows cross-sensitivity reactions (Ref. 13).

Adriani and Campbell (Ref. 2) and Adriani (Ref. 3) have repeatedly emphasized the clinical hazards of cocaine and tetracaine to tracheal tissues. There are no known data on the use of tetracaine in the rectum. Based on absorption through other mucous membranes (Refs. 2, 3, and 11), it is probably absorbed from the rectal mucosa and thus into the systemic circulation. Therefore, the safety of tetracaine when used intrarectally remains to be established.

(4) *Effectiveness (external use).* Tetracaine hydrochloride is used to produce local anesthesia of the sclera, conjunctiva and mucous membranes (Ref. 3). Commercial products containing 0.5 to 2.0 percent tetracaine in ointment are used topically on minor burns and scalds, skin ulcers, and sunburn to relieve itching (Ref. 13) but have not been studied in the anorectal area. Clinicians have relied largely on subjective studies and clinical impressions rather than controlled studies in assessing the effectiveness of topical anesthetics. Using the Adriani technique (Refs. 14 and 15) of electrical stimulation to elicit cutaneous itch and pain without apparent injury to the skin, it was demonstrated that saturated solutions of tetracaine in water, 40 percent alcohol and 10 percent glycerin were effective on sunburned skin. None of the manufactured preparations tested completely blocked the sensation of itch and burning on intact skin stimulated electrically, with the exception of 20 percent benzocaine in polethylene glycol ointment (Refs. 14 and 15).

A 1 percent solution of tetracaine topically is as effective as a 10 percent solution of procaine when applied directly to a nerve trunk (Ref. 2). Stronger solutions have been used but no proof exits to show increased strength produces increased effects. Increased strength will produce increased toxicity. Therefore, the Panel concludes effectiveness has yet to be proven.

(5) *Effectiveness (intrarectal use).* No studies were found that relate to the intrarectal effectiveness of tetracaine. The effectiveness of tetracaine in this area, where no pain sensation is experienced, must be proven.

(6) *Proposed dosage.* Adult external and intrarectal dosage is 10 to 20 mg per dosage unit up to five times daily and not to exceed 100 mg per 24 hours.

(7) *Labeling.* The Panel recommends the Category I labeling for local anesthetic active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(8) *Evaluation.* The Panel questions the use of a local anesthetic in an area above the anorectal line (in the rectum) where there are no pain sensory nerve fibers, and concludes that there is insufficient evidence at this time to recommend tetracaine as effective for intrarectal use in OTC anorectal preparations.

To prove that tetracaine is effective externally or intrarectally for use in OTC anorectal products, testing must be performed. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the following claims.

Claims such as "prompt" and "quick acting" imply an activity that takes effect within 20 minutes; however, the data presented to the Panel are insufficient to substantiate a so-called "prompt" or "quick" action. Therefore, the Panel concludes that these claims as well as unspecified time claims such as "for hours" are indeterminate and not allowed until clinical study can correlate a specific time in minutes or hours for said claims. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

IV. Vasoconstrictors

A. General Discussion

The Panel defines a vasoconstrictor as an agent that causes temporary constriction of blood vessels. Although many substances constrict blood vessels, only those sympathetic vasoconstrictors used in OTC anorectal products were considered by the Panel. Sympathomimetic vasoconstrictors, hereafter referred to as vasoconstrictors, are chemical agents that are structurally related to the naturally occurring catecholamines, epinephrine, and norepinephrine (Ref. 1). These agents act as neural transmitters by carrying stimuli or messages from nerves to receptors in various parts of the body so that specific parts of the body will respond in some specific way (Ref. 2).

Vasoconstrictors attach to alpha and/or beta adrenergic receptors (Refs. 3 and 4). Alpha receptors are found in vascular beds, especially in arterioles (small arteries) and capillaries, where stimulation causes constriction. Beta receptors are found primarily in cardiac muscle where stimulation may cause increased force and rate of contraction of the heart (Refs. 1, 3 and 4). Beta receptors are also found in pulmonary muscles where stimulation causes relaxation of bronchial spasm (Refs. 1, 3 and 4). It is important to remember that a concomitant effect occurs on beta receptors in the heart and lungs when vasoconstrictors are applied to alpha receptors in the anorectal area.

The Panel has reviewed the available data and has included only three

vasoconstrictors within this document based on products submitted for review. Epinephrine stimulates both alpha and beta receptors. Ephedrine stimulates both alpha and beta receptors and, in addition, initiates the release of body stores of norepinephrine and indirectly produces an additional alpha receptor response. Phenylephrine has only alpha stimulating properties (Refs. 1 and 4). The response of blood vessels to epinephrine, ephedrine, and phenylephrine varies throughout the body, but the blood vessels to skin and mucous membranes are constricted by these drugs that act on their alpha receptors (Ref. 1). This vasoconstrictive effect on dilated skin vessels has been used in OTC products to treat congestion of nasal mucous membranes and has also been used to aid in control of minor bleeding (Refs. 1 and 5). However, the Panel concludes that claims for control of minor bleeding are not appropriate for OTC anorectal use and if bleeding occurs, a physician should be consulted.

Anorectal disorders include many ailments but hemorrhoids are now of the most common. Historically, hemorrhoids are believed to be an abnormal cluster of dilated veins, and the cause of hemorrhoids is believed to be venous stasis or blockage (Refs. 5 through 9). Recent studies indicate hemorrhoidal vessels may be arterio-venous anastomoses which are described as wide-bore connecting channels between the larger vessels (Refs. 9 and 10). Some investigators believe hemorrhoids resemble, anatomically, the corpus cavernosum of the penis and call the hemorrhoids corpus cavernosum recti (Refs. 8 and 11). Both corpuses can fill rapidly with blood and empty, but not with equal speed. Anatomical and radiological studies of injected specimens show similar structures called "bodies" (corpus) in normal patients as well as in those patients having hemorrhoids (Refs. 9 and 11). A new explanation for the cause of hemorrhoids is a downward slide of the anal canal lining which includes these "bodies" or arterio-venous anastomoses (Refs. 8 and 9). Oxygen content of blood from hemorrhoidal veins was studied by Thulesius and Gjores (Ref. 10) and was found to equal the oxygen content of central arteries and to far exceed the oxygen content of central and peripheral veins. The presence of this level of oxygen may explain the bright red or arterial type of bleeding described by patients and seen by surgeons. In this same study, blood flow measurements with a thermocouple in the anal canal demonstrated prompt response of mucosal perfusion by the topical application of vasoconstrictors which would be expected only if arterioles are present; venules do not respond to vasoconstrictors (Ref. 10).

Vasoconstrictors are reported to give relief of local itching by a minimal anesthetic effect (Ref. 12). This may be due to the same phenomenon; i.e., vasoconstriction of blood vessels of the skin, or it could be due to the chemical structure of vasoconstrictors which resembles that of local anesthetics (Refs. 1 and 4). The exact mechanism of this anesthetic effect is unknown, but the Panel recognizes the relief of itching by vasoconstrictors.

Because rectal absorption of an ingredient varies with the vehicle and pH of the rectum (Ref. 13), excessive or repeated dosing greater than 7 days may permit absorption of significant amounts of these agents into the bloodstream via the hemorrhoidal vessels, which can produce systemic effects.

Due to potential serious side effects of these agents and because useful effects are achieved with minimum quantities, the Panel has chosen to limit safe OTC dosages to safe intravenous dosages.

When used in recommended safe dosage for local effect, undesirable systemic effects can be avoided. These undesirable side effects can include elevation of blood pressure, cardiac arrhythmia or irregular heart rate, central nervous system disturbance or nervousness, tremor, sleeplessness, and aggravation of symptoms of hyperthyroidism (Refs. 1 and 4). Prolonged use of excessive dosage can lead to anxiety or paranoia (Ref. 4). More commonly, prolonged use of the correct dosage will lead to rebound vasodilatation and congestion, which is discussed in the findings of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products as published in the **Federal Register** of September 9, 1976 (41 FR 38396). This adverse effect on nasal mucous membranes is well-established, but there are no similar studies related to rectal mucous membrane, only the theoretical implications. Contact dermatitis following topical use of some vasoconstrictors has been reported (Ref. 14). Vasoconstrictors, if absorbed, can interact with monoamine oxidase inhibitors, which are used for mental depression (Refs. 1 and 4). The hypertensive effects of the vasoconstrictors may be potentiated by these psychotherapeutic agents and combined use can lead to serious, even lethal effects, such as a cerebral hemorrhage or a stroke (Refs. 1, 4, 15, and 16). Therefore, the Panel concludes that a caution as provided under labeling for products containing Category I vasoconstrictors is appropriate. (See part IV. paragraph B.1. below—Category I Labeling.)

The Panel concludes that sympathomimetic vasoconstrictors do cause constriction of the vascular bed in skin and mucous membrane in other parts of the body and can give a subsequent decongestive effect. The Panel recognizes partial relief of local itching is achieved by topical application of vasoconstrictors. The Panel recognizes that vasoconstrictors can be used for other reasons and that there are more effective agents for relief of local itching.

The Panel does not recognize or approve the use of vasoconstrictors for the control of minor bleeding. As bleeding may be a sign of conditions ranging from abrasions to cancer, the Panel concludes that conditions evidenced by bleeding should not be self-medicated and that the advice and supervision of a physician should be obtained. Therefore, the warning is warranted: "In case of bleeding, consult a physician promptly." (See part II. paragraph Q.5 above—Warnings.)

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B. Categorization of Data

1. *Category I conditions under which vasoconstrictor ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

The Panel has classified the following vasoconstrictor active ingredients as generally recognized as safe and effective and not misbranded:

Ephedrine sulfate in aqueous solution (external and intrarectal use) Epinephrine hydrochloride in aqueous solution (external use)

Phenylephrine hydrochloride in aqueous solution (external and intrarectal use)

a. *Ephedrine sulfate in aqueous solution (external and intrarectal use).* The Panel concluded that 2 to 25 mg ephedrine sulfate in aqueous solution per dosage unit is safe and effective for external and intrarectal use as a vasoconstrictor in OTC anorectal preparations up to four times daily and not to exceed 100 mg 24 hours.

(1) *Description.* Ephedrine sulfate, a fine white odorless crystal or power, is freely soluble in water and soluble in oil (Refs. 1 and 2). The aqueous solution is stable but is decomposed by exposure to light or heat. Solutions of 1 to 3 percent and 1 percent jelly are used as a nasal decongestant. Solutions of 3 to 5 percent have been used in the eye for mydriasis since 1895 (Ref. 3).

(2) *Safety.* Ephedrine sulfate is readily absorbed from the mucous membrane of the intestinal tract, including the rectum (Refs. 2, 3, and 4). In humans, this drug is excreted unchanged by the kidneys. Within 12 hours, 60 to 75 percent of the administered dose is excreted and approximately 100 percent is excreted in 24 hours (Ref. 3).

Drugs used in the anorectal area are in contact with normal and/or inflamed skin and rectal mucosa. Absorption depends on many factors. It varies from the same rate as intravenous injections to slower than oral absorption rates (Refs. 1 and 5) which require a larger quantity of drug to produce the desired effect. The Panel has chosen to equate safe OTC doses with safe intravenous doses because useful effects are obtained with a minimum quantity of drug. This approach provides a more desirable margin of safety if the consumer inadvertently or deliberately uses this ingredient in excess of the recommended dosage (Refs. 6, 7, and 8).

Published data on animals and humans relating to clinical reports of toxic reactions to ephedrine sulfate are discussed in the findings of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products as published in the **Federal Register** of September 9, 1976 (41 FR 38397). This data involves intravenous, intramuscular, and oral administration of ephedrine sulfate. There are significant undesirable effects with oral doses of ephedrine above 50 mg which include nervousness, insomnia, tremulousness, vertigo, headache, tachycardia, palpitation, and diaphoresis (Ref. 2). Otherwise safe doses of 15 to 50 mg may be dangerous if totally absorbed by patients who have hyperthyroidism, hypertension, or angina pectoris, or by patients taking digitalis for heart conditions (Refs. 2 and 9). Ephedrine has a more prolonged effect than epinephrine and both alpha and beta adrenergic effects. Chronic use of ephedrine may lead to anxiety and/or a paranoid state in adults (Ref. 6).

The hypertensive effects of ephedrine are potentiated by monoamine oxidase (MAO) inhibitors, as well as tricyclic antidepressants. Combined use can lead to serious, even lethal effects (Refs. 1 and 2). MAO inhibitors prolong sympathomimetic effect by delaying inactivation of the catecholamine norepinephrine. As a result, increased pressure develops in the blood vessels and cerebral (subarachnoid) hemorrhages or strokes have been reported with the use of MAO inhibitors and ephedrine sulfate at various dosage levels (Refs. 1 and 2). Contact dermatitis following topical use of ephedrine sulfate has been reported (Ref. 10). Also of importance is the fact that ephedrine sulfate antagonzies the tranquilizing effects of phenothiazines (Ref. 2). A warning about these agents is needed to alert persons against using this product without consulting a physician if they have heart trouble, thyroid disease, are taking digitalis or heart medicine, or are taking antidepressants or other psychotherapeutic drugs. With the above exceptions, available experimental data on the effect of ephedrine sulfate in animals and in humans indicate that it is safe for external use whether skin is abraded or intact when used in recommended dosages (Ref. 2). In persons free of the above diseases and not taking the above medications, ephedrine sulfate is considered a safe vasoconstrictor for internal and external anorectal application provided the dosage is limited to 2 to 3 sprays or drops of 0.5 to 1.0 percent, not more often that every 4 hours. Rebound congestion can occur with higher dosages (Refs. 2 and 7). This dosage is discussed in the September 9, 1976 document at page 38397.

(3) *Effectiveness.* With topical application of aqueous solution on nasal mucosa, the onset of action of ephedrine sulfate is from a few seconds to 1 minute, and the duration of its effectiveness may persist up to 2 to 3 hours as discussed in the September 9, 1976 document at page 38397. Vasoconstriction of capillaries and arterioles follows topical application of ephedrine sulfate to abraded skin as well as mucosa (Ref. 2 and 3). As a result, there is a decongestant effect and some reduction in swelling. Local relief of itching or minimal anesthetic properties are also reported (Refs. 4 and 11). Ephedrine has been used as an oral sympathomimetic and a topical nasal decongestant of low toxicity (Refs. 1, 2, 3, and 12). The therapeutic value of ephedrine sulfate is based on its ability to constrict arterioles, which is the mechanism by which it produces a decongestant effect. There has been no evidence to support vasoconstrictor effect on veins (Ref. 13). Ephedrine sulfate has been shown to be effective in the control of arteriolar bleeding (Ref. 2). Thulesius and Gjores (Ref. 14) have shown hemorrhoids to be a mixture of arterioles and venules (arterio-venous anastomoses) with blood oxygen content similar to central and peripheral arteries. Thus, this drug can constrict vessels and, therefore, decrease blood flow in the arterioles or capillaries and reduce the volume of blood delivered to the veins, although this effect has not been demonstrated on hemorrhoidal

vessels. Use of vasoconstrictors in the anorectal area has been found by thermocouple measurements to reduce blood flow (Ref. 14). If applied repetitively, ephedrine may lead to rebound congestion (Ref. 2). The Panel concludes that ephedrine is effective for the temporary relief of swelling in the anorectal area.

It appears reasonable that ephedrine sulfate in an ointment would provide better surface contact and greater effectiveness, but formulation sharply affects the ability of the active ingredient to be released to the skin or mucosa (Refs. 15 and 16). Neither a literature survey nor review of the submitted data provided effectiveness studies on a final formulation of ephedrine sulfate in an ointment.

The pharmcology of ephedrine is similar to epinephrine (Ref. 3). Topical application of epinephrine on intact skin to produce blanching will prevent pruritus due to histamine (Ref. 11). The chemical structure of vasoconstrictors is related to local anesthetics. Vasoconstrictors have been shown to exert some local anesthetic effect (Refs. 1, 2, and 11). Therefore, the Panel concludes that ephedrine sulfate in aqueous solution is effective as an antipruritic.

The effective dosage of ephedrine sulfate as a mucosal decongestant ranges from 0.5 to 1.0 percent (5 to 10 mg/mL in aqueous solution) or a maximum of 3 mg per dosage unit every 4 hours as also discussed in the September 9, 1976 document at page 38397.

(4) *Dosage.* Adult external and intrarectal dosage is 2 to 25 mg ephedrine sulfate in aqueous solution per dosage unit up to four times daily and not to exceed 100 mg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for vasoconstrictor active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

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b. *Epinephrine hydrochloride in aqueous solution (external use).* The Panel concludes that 100 to 200 micrograms (μg) epinephrine hydrochloride in aqueous solution per dosage unit is safe and effective for use up to four times daily and not to exceed 800 μg per 24 hours.

(1) *Description.* Epinephrine is a short acting sympathomimetic agent. It is obtained either from the adrenal glands of animals or by chemical synthesis. It is a white powder, very slightly soluble in water and alcohol. It is insoluble in chloroform and ether. The levorotatory drug occurs naturally and is 15 times more active than the destrorotatory form. The racemic mixture has less activity, depending an the ration of levorotatory-to-dextrorotatory ephinephrine present. Epinephrine is assayed in terms of its content of the levorotatory form.

In solution epinephrine is readily oxidized and becomes inactive. Stability is enhanced in acid, but epinephrine deteriorates rapidly in alkaline solution (Refs. 1 and 2).

(2) *Safety.* In adults an increase in blood pressure follows the intramuscular injection of 1 to 5 μg (Ref. 3). The minimum lethal dose of epinephrine hydrochloride administered subcutaneously is presumed by Grollman and Grollman (Ref. 3) to be about 10,000 micrograms/kilogram (μg/kg) of body weight. The intravenous injection of as little as 300 μg has produced alarming symptoms in humans (Ref. 3). The chief hazards of intravenous injection above 500 μg are increased risk of stroke because of increased blood pressure, purmonary edema, and cardiac arrhythmias (Ref. 4). However, for acute asthma unresponsive to other drugs, large doses are tolerated, e.g., intravenous injection of 150 μg every 15 to 60 seconds has been used (Ref. 1). Because of similar chemical structure, undesirable effects of epinephrine hydrochloride described above are the same as for ephedrine sulfate. (See part IV. paragraph B.1.a. above—Ephedrine sulfate in aqueous solution (external and intrarectal use).)

Forsyth et al. (Ref. 5) have demonstrated with C–14 systemic absorption through mucous membrane of 23.8 to 91.5 percent (238 μg to 915 μg) of racemic epinephrine-C-14 hydrochloride in aqueous solution applied to fresh gingival lacerations in anesthetized Rhesus monkeys by means of gingival retraction strings. Concomitant elevation of systolic and diastolic pressures and of pulse rates from 4 to 18 percent were observed in their experiments. OTC preparations contain only a fraction (100 μg/g of ointment) of the epinephrine used in the Forsyth et al. study (Ref. 5), but these preparations do contain an amount similar to that used for the treatment of asthma.

When used externally in anorectal preparations such as an ointment, it would be highly unlikely that venous absorption would reach a toxic level, and any effect would be of short duration (Ref. 6). When epinephrine hydrochloride in aqueous solution is applied locally to intact skin, it usually produces such intense vasoconstriction that systemic absorption in prevented (Ref. 3). However, when a suppository or ointment is placed within the rectum that may be inflamed or have lesions on the mucosal lining, conceivably absorption of epinephrine could be rapid (Ref. 5) and if used alone could approach blood levels similar to those obtained with intravenous injections. Although there is some evidence that in

the presence of a bland vehicle absorption will be slowed, until proved otherwise, 100 percent absorption is assumed to provide an adequate safety margin in OTC products. (See part II. paragraph G. above—Bioavailability of Anorectal Dosage Forms.)

Because of these safety considerations, the Panel has set the upper limit of epinephrine hydrochloride in aqueous solution in OTC anorectal preparations for external and internal use at 200 μg per dosage unit.

(3) *Effectiveness.* The known therapeutic uses of epinephrine hydrochloride are to constrict arterial blood vessels of the skin, stimulate the heart, relax bronchioles, and induce glycogenolysis (Ref. 3). For anorectal disease, only vasoconstriction is of importance because of the resultant reduction of swelling that theoretically will follow a reduction in blood flow to the anorectal area (Ref. 7). Other effects can be to reduce pruritus and reduce swelling. When combined with local anesthetics for use by injections (Refs. 1 and 3), epinephrine hydrochloride in a concentration of 0.0005 percent (5 μg/mL) (Ref. 1) is generally sufficient to limit the absorption of local anesthetics, and this effect prolongs the effect of the anesthetics. Although a solution equivalent to 2 percent epinephrine base in a dosage form designed to deliver 1,000 μg/drop is used in the conjunctiva for glaucoma (Refs. 4 and 8), the concentration is rapidly reduced by lacrimal fluid and tearing. In the treatment of anorectal symptoms, epinephrine constricts arterioles, and the Panel concludes that this will decrease swelling of tissues; however, degradation of epinephrine due to the alkaline pH of the rectum is considered sufficient to reduce its effectiveness. The Ph of the rectum is 8 to 10 in some cases of pruritus and is rarely below 6 (Ref. 9). Epinephrine is extremely unstable and requires a buffered solution of pH 4.2 to remain stable (Ref. 10). It is possible that salts of epinephrine such as epinephrine undecylenate (Ref. 11) are effective, but there are no data to establish safety or effectiveness.

The Panel concludes that in the dosage recommended epinephrine hydrochloride in aqueous solution is safe for external and intrarectal use. It is effective for the temporary relief of itching and swelling when applied externally. Because it is inactivated by the alkaline secretions of the rectum, the Panel concludes that epinephrine hydrochloride is not active intrarectally. For the reduction of congestion and swelling, it has been used locally on the conjunctiva and to reduce nasal congestion (Ref. 1). However, in the latter case because of its secondary vasodilation effect, swelling may not respond or may even be greater than that initially observed (Ref. 1). Though it has been used in a 0.1 percent (1,000 μg/mL) solution for topical application and in suppositories (Ref. 1), the Panel did not receive any controlled studies indicating its value in OTC anorectal preparations and the recommendations are based on aqueous solutions used in the data.

Melton and Shelley (Ref. 12) found that the topical application of epinephrine hydrochloride in aqueous solution to the intact skin in sufficient quantity produced blanching and that it was impossible to produce pruritus in such an area by the subcutaneous injection of histamine. Histamine injected locally in normal skin routinely produced pruritus. These observations suggest that it is effective in the treatment of pruritus due to histamine release. Clinical studies have shown that it is effective to relieve certain itching dermatoses of the skin (Ref. 11). Epinephrine undecylenate ointment used in these studies was claimed effective to relieve itching only when the epidermis was abraded (Ref. 11). The safety and effectiveness of this form of epinephrine are discussed below. (See part IV. paragraph B.3.b. below—Epinephrine undecylenate (external use).)

The Panel concludes that epinephrine hydrochloride in aqueous solution having a concentration of 0.1 percent (1,000 μg/mL) is safe and effecive for temporary relief of itching and swelling of hemorrhoidal tissues.

Though local application is effective in providing vasoconstriction and cessation of bleeding that may result from irritation or excoriation, the Panel has concluded that no claims for control of bleeding can be made by OTC products.

(4) *Dosage.* Adult external dosage is 100 to 200 μg epinephrine hydrochloride in aqueous solution per dosage unit up to four times daily and not to exceed 800 μg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for vasoconstrictor active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

References

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(8) OTC Volume 120002, p. 71.

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(11) OTC Volume 120002.

(12) Melton, F. M. and W. B. Shelley, "The Effect of Topical Antipruritic Therapy on Experimentally Induced Pruritus in Man," *The Journal of Investigative Dermatology,* 15:325–332, 1950.

c. *Phenylephrine hydrochloride in aqueous solution (external and intrarectal use).* The Panel concludes that 0.5 mg phenylephrine hydrochloride in aqueous solution per dosage unit is safe and effective for use as a vasoconstrictor in OTC anorectal preparations for external and intrarectal use up to four times daily and not to exceed 2 mg per 24 hours.

(1) *Description.* Phenylephrine hydrochloride is structurally related to norepinephrine. it is a potent alpha adrenergic stimulant with little effect on the central nervous system. Phenylephrine, in contrast to epinephrine and ephedrine, reflexly slows the heart rate and increases the stroke output, but does not disturb cardiac rhythm. Its primary action is to produce vasoconstriction by a direct effect on receptors rather than by norepinephrine displacement. It is used parenterally, orally, and topically to produce generalized or nasal vasoconstriction (Refs. 1 and 2) and by injection to prolong the effects of local anesthetics (Ref. 3).

(2) *Safety.* The safety of phenylephrine hydrochloride decreases as the dose is increased, due to its ability to cause general arterial constriction and hypertension (Refs. 1 and 2). It is reportedly less likely to produce local irritation than other vasoconstrictors (Ref. 4). Systemic effects often increase in persons with

hyperthyroidism, hypertension, or cardiovascular disease, and in those persons who take certain antidepressant drugs such as monamine oxidase inhibitors and tricyclic antidepressants (Refs. 5 and 6). (See part IV. paragraph A. above—General discussion.) The amount of this drug absorbed from the rectal area is unknown, but the potential for complete systemic absorption through the hemorrhoidal veins would require that no more than the intravenous dose (0.5 mg) producing systemic effects (Ref. 2) be allowed for intrarectal application, despite the uncertainty of incomplete bioavailability from various vehicles. Accordingly, no more than 0.5 mg phenylephrine hydorchloride per application four times daily should be used (Ref. 2). As with any of the sympathomimetics described in this document, it should not be used in persons with the above described diseases or who are taking the above noted drugs.

(3) *Effectiveness.* Phenylephrine hydrochloride is a very efficient arteriolar constrictor (Refs. 1 and 2) and a nasal decongestant at 0.25 to 0.5 percent in aqueous solution, as described in the findings of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products as published in the **Federal Register** of September 9, 1976 (41 FR 38399). Studies of its effects on venous beds found the effects to be minimal (Refs. 1, 2, and 7), but no studies of its effects on the hemorrhoidal area were found. although some sources state that there is no evidence demonstrating the effectiveness of vasoconstrictors on hemorrhoidal veins (Refs. 7 and 8), the Panel concludes that phenylephrine hydrochloride has a beneficial effect on swollen hemorrhoidal tissue by virtue of reduction of capillary and arterio-venous congestion in the anorectal area (Refs. 9 and 10).

Phenylephrine hydorchloride is pharmacologically very similar to epinephrine. Temporary relief of itching produced by histamine has been secured after topical administration of epinephrine (Ref. 11). The Panel concludes that although no data are available, a similar effect may be claimed for phenylephrine.

In view of the unpredictable effects of final formulation on the ingredient, the effectiveness of phenylephrine hydrochloride in any final formulation other than an aqueous solution, such as suppositories, is discussed elsewhere in this document. (See part IV. paragraph B.3.c. below—Phenylephrine hydorchloride suppositories (intrarectal use) and part II. paragraph G. above—bioavailability of Anorectal dosage Forms.)

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. No other effective dose is known at this time; therefore, there is no basis for considering a dose other than 0.5 mg to be effective.

In summary, phenylephrine hydrochloride, in the recommended dosage, is safe and effective for external or intrarectal use for the temporary relief of swelling or itching in the anorectal area.

(4) *Dosage.* Adult external and intrarectal dosage is 0.5 mg phenylephrine hydrochloride in aqueous solution per dosage unit up to four times daily and not to exceed 2 mg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for vasoconstrictor active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

References

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(10) OTC Volumes 120013 and 120014.

(11) Melton, F. M. and W. B. Shelley, "The Effect of Topical Antipruritic Therapy on Experimentally Induced Pruritis in Man," *The Journal of Investigative Dermatology,* 15:325–332, 1950.

Category I Labeling

The Panel recommends the following Category I labeling for vasoconstrictor active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indications.* (1) "Temporarily reduces the swelling associated with irritated hemorrhoidal tissue and other anorectal disorders."

(2) "Temporarily reduces the swelling associated with irritation in hemorrhoids and other anorectal disorders."

(3) "Temporarily shrinks hemorrhoidal tissue."

(4) "May temporarily relieve itching."

b. *Warning.* "Do not use this product if you have heart disease, high blood pressure, hyperthyriodism, diabetes, difficulty in urination, or are taking tranquilizers or nerve pills."

2. *Category II conditions under which vasoconstrictor ingredients or not generally recognized as safe and effective or are misbranded.* The Panel recommends that Category II conditions be eliminated from OTC anorectal products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

The Panel has classified the following vasoconstrictor active ingredients as not generally recognized as safe and effective or as misbranded:

Epinephrine hydrochloride (intrarectal use)
Epinephrine undecylenate (intrarectal use)
Epinephrine hydrochloride and epinephrine undecylenate (intrarectal use).

The Panel concludes that epinephrine hydrochloride and epinephrine undecylenate are safe but not effective intrarectally for use as a vasoconstrictor in OTC anorectal preparations.

(1) *Description.* (See part IV. paragraph B.1.b.(1) above—Description.)

(2) *Safety.* (See part IV. paragraph B.1.b.(2) above—Safety.)

(3) *Effectiveness.* The Panel concludes that intrarectal use of epinephrine hydrochloride and epinephrine undecylenate are not effective. Epinephrine is rapidly decomposed in alkaline solutions (Refs. 1 and 2). The pH of the rectum is normall greater than six (Ref. 3). Therefore, upon release of epinephrine from any final formulation, based on the data reviewed by the Panel, these ingredients are immediately rendered ineffective.

(4) *Evaluation.* The Panel concludes that the intrarectal use of epinephrine hydrochloride and epinephrine undecylenate are not effective at any

does submitted to the Panel, although they are safe at the dosage recommended for OTC anorectal products.

References

(1) "The United States Dispensatory and Physician's Pharmacology," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 475–477, 1973.

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Category II Labeling.

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of vasoconstrictor drug products are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claims to be misleading and unsupported by scientific data.

The claim that certain combinations of ingredients may be used to "shrink hemorrhoids" or to "shrink Hemorrhoidal tissue" has been made. The applicability of such a claim must rest primarily on a definition of the word "shrink."

According to Webster's dictionary, the word several meanings. There is general agreement that it refers to a reduction in size. However, opinions differ as to whether this signifies a temporary phenomenon or implies a permanent change.

The public is likely to consider that a permanent change is to be expected. However, data presented on vasoconstrictors indicate a temporary reduction in swelling but in the long run rebound swelling may occur. Therefore, to "shrink hemorrhoids" or "shrink hemorrhoidal tissue" is not achievable with OTC anorectal products and is misleading. The Panel concurs that vasoconstrictors can "temporarily reduce swelling" or "temporarily shrinks" and finds these words sufficiently strong to convey the usefulness of this class of ingredients in the short term treatment of anorectal symptoms. (See part IV. paragraph B.1. above—Category I Labeling.) Consumers with any persistent symptom should seek the advice of a physician.

The claim "control of minor bleeding" implies the ability on the part of the consumer to decide whether or not to seek medical attention based on knowing how to distinguish between blood originating from abrasions or irritations resulting from such activities as scratching or excessive rubbing with coarse toilet paper and blood originating from more serious lesions such as fissures and carcinoma. The quantity of bleeding cannot serve as an indicator of the seriousness of the condition, especially in the early stages of disease. Early detection of carcinoma is still the best available means of control, and this is best encouraged, in the opinion of the Panel, by directing the user of anorectal drug products to consult the physician if bleeding occurs for any reason. (See part II paragraph Q.5. above—Warnings.)

"Provides prompt and prolonged decongestion and vasoconstriction" implies complete and final relief and is considered misleading.

3. *Category III conditions for which the avaialable data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the vasoconstrictor active ingredients listed below. The Panel believes that it is reasonable to provide 2 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained with 2 years, however, the ingredients listed in this category should no longer be marketed in OTC products:

Epinephrine (external and intrarectal use)
Epinephrine undecylenate (external use)
Phenylephrine hydrochloride suppositories (intrarectal use)

a. *Epinephrine (external and intrarectal use).* The Panel concludes that there are insufficient data to establish the safety or effectiveness of epinephrine for external or intrarectal use as a vasoconstrictor in OTC anorectal preparations.

(1) *Description.* (See part IV. paragraph B.1.b. (1) above—Description.)

(2) *Safety.* The safe use of the epinephrine moiety is discussed in depth earlier in this document. (See part IV. paragraph B.1.b.(2) above—Safety.)

(3) *Effectiveness.* The effectiveness of epinephrine hydrochloride in aqueous solution has been established. (See part IV. paragraph B.1.b.(3) above—Effectivness.) Epinephrine in the base form is not soluble in water, and therefore, the Panel concludes that the effectiveness of epinephrine base has not been established.

(4) *Proposed dosage.* Adult external dosage is 100 to 200 μg per dosage unit up to four times daily and not to exceed 800 μg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for vasoconstrictor active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* Data to demonstrate safety and effectiveness as an anorectal ingredient will be required in accordance with the guidelines set forth earlier in this document. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

b. *Epinephrine undecylenate (external use).* The Panel concludes that there are insufficient data to establish the safety or effectiveness of epinephrine undecylenate.

(1) *Description.* Epinephrine undecylenate is presumed to be a short acting sympathomimetic agent, chemically, an ester of epinephrine base (Ref. 1).

(2) *safety.* The safe use of the epinephrine moiety is discussed in depth earlier in this document. (See part IV. paragraph B.1.b.(2) above—Safety.) The safe use of epinephrine undecylenate remains to be established, although experimental evidence implies a degree of safe use (Ref. 1).

(3) *Effectiveness.* The effectiveness of the epinephrine moiety in a final formulation has been discussed in depth earlier in this document. (See part IV. paragraph B.1.b.(3) above—Effectiveness.) The Panel does not have sufficient data to establish effectiveness of epinephrine undecylenate, nor is there sufficient evidence that this ingredient in final formulation becomes available and effective at the site of action (Ref. 1). (See part II. paragraph G. above—Bioavailability of Anorectal Dosage Forms.)

(4) *Proposed dosage.* Adult external dosage is 100 to 200 μg per dosage unit up to four times daily and not to exceed 800 μg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for vasoconstrictor active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* Data to demonstrate safety and effectiveness as an anorectal ingredient will be required in accordance with the guidelines set forth earlier in this document. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

Reference

(1) OTC Volume 120002, p. 47.

c. *Phenylephrine hydrochloride suppositories (intrarectal use).* The Panel concludes that phenylephrine hydrochloride is safe at the recommended dosage but there are insufficient data to establish effectiveness in the final formulation.

(1) *Description.* Phenylephrine hydrochloride is a potent alpha adrenergic stimulant. (See part IV. paragraph B.1.c.(1) above—Description.)

(2) Safety. (See part IV. paragraph B.1.c.(2) above—Safety.)

(3) *Effectiveness.* The effectiveness of phenylephrine hydrochloride as a vasoconstrictor in aqueous solution cannot be extrapolated to include effectiveness in final formulation as a suppository (Ref. 1) because there are insufficient data. (See part IV. paragraph B.1.c.(3) above—Effectiveness.)

(4) *Proposed dosage.* Adult intrarectal dosage is 0.5 mg per suppository up to four times daily, not to exceed 2 mg per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for vasoconstrictor active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* The Panel concludes that pheynlephrine hydrochloride in a suppository dosage final formulation as submitted to the Panel is safe at the recommended dosage but must be evaluated for effectiveness in accordance with the guidelines set forth above for testing anorectal ingredients. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

Reference

(1) OTC Volume 120013 and 120014.

Category III Labeling

None.

V. Protectants

General Discussion

The Panel has defined protectants as agents that provide a physical barrier, forming a protective coating over skin or mucous membranes. Varying quantities of these agents are useful as pharmaceutical necessities, e.g., vehicles and stiffening agents, in the formulation of anorectal dosage forms, e.g., ointments, lotions, creams, suppositories, and dusting powders.

Protectants include absorbents, adsorbents, demulcents, and emollients.

Absorbents are agents that take up within themselves fluids or other substances on or secreted by the skin or mucous membranes. This definition could apply to materials such as cotton or toilet paper which absorb body tissue fluid and mucus, however, for purposes of this review, the definition applies only to ingredients submitted to the Panel for review.

Absorbents are agents that because of a fine state of subdivision, are capable of attaching to substances that are secreted by the skin or mucous membranes.

Demulcents are defined as agents that combine with water to form a physical relationship between molecules that are called colloidal solution; the cohesiveness of these solutions containing demulcents have the capacity to protect skin surfaces in a manner similar to that of mucus.

Emollients are defined as agents used to soften or protect internal or external body surfaces. They are substances derived from animal or vegetable fats or petroleum products. Some of the substances are water soluble and others are oil soluble (Ref. 1). By virtue of their physical nature, which allows homogeneous spreading over tissue surfaces, they can form a protective coat over affected areas, aid in softening dehydrated or injured areas by preventing tissue water loss (Refs. 2 and 3), and tend to counteract symptoms and signs of drying skin (Refs. 2 and 4). This group also includes some substances such as glycerin which bind water tightly, but also fit the definition of emollients (Ref. 1). In the therapy of anorectal problems, emollients should be avoided because they can produce blockage of hair follicles and gland ducts (Refs. 5, 6, and 7). Many agents with emollient effects are also used as vehicles, bases, or carriers for pharmacologically active agents, and the Panel recognizes the dual purpose of their use (Refs. 1 and 8).

As a general rule, protectants are not absorbed through intact or broken skin or mucous membranes. The majority of ingredients considered in this section are relatively inert and are safe regardless of the amount that is applied to the anorectal area. Absorption can occur with the bismuth compounds, so these ingredients may be unsafe and will be discussed later within this section. Allergic reactions may occur with certain ingredients such as wool alcohols, and these are also identified and discussed later.

In determining the effectiveness of these agents, the Panel has concluded that protectants, alone or in combination, are of therapeutic value by providing a physical barrier that prevents irritation of anorectal tissue. A second action of protectants is to prevent water loss from the stratum corneum of the skin.

The Panel believes that the concept of protectants providing a physical barrier over anorectal tissue and preventing further insult is reasonable and useful. The barrier effect of protectants is supported by data indicating that infant perianal skin is afforded significant protection against diaper wetness by application of a continuous film of petrolatum applied to the skin in the diaper area (Ref. 6).

The effectiveness of protectants in providing an occlusive film that prevents transepidermal water loss has been reported (Refs. 10 and 11). For example, data have been presented to the Panel (Ref. 12) indicating that the occlusive thickness needed to reduce water loss to zero ranged from a low of 0.26 mm for light mineral oil to a high of 0.96 mm for a cream consisting of only 24 percent protectants (or 33 percent total emollients and humectants). Thus, assuming an average dose of 2 g, when petrolatum (which has a specific gravity of 0.8) is applied topically over an area of 36 cm^2, which is approximately equal to the perianal skin surface, it would result in a film thickness of 0.65 mm. However, such a film will not stay in place if a protective ingredient is a liquid of very low viscosity or is a powder (Ref. 12). Furthermore, when applied to the anorectal area, a protectant is subject to removal by clothing, as well as during and after bowel movement. The importance of water in the outer layer (stratum corneum) of the skin has been well established (Ref. 7). Drying of the stratum corneum may be a cause of itching, pain, and/or burning (Ref. 1). It is the Panel's opinion that irritants, whether incurred by the use of toilet tissue or inadequate cleansing of fecal material, will also aggravate these symptoms.

The Panel further concludes that to justify a claim for protective effect, either of the following criteria must be met: (1) At least one protectant must be present in at least 50 percent (1 g) of a 2-g dosage unit, or (2) a combination of two but not more than four protectants must be present for a combined concentration of at least 50 percent (1 g) of a 2-g dosage unit. For those protectant ingredients limited to concentrations of less than 50 percent, they may be used only in combination with other protectants.

This conclusion was based on the Panel's determination of an adequate quantity of an ingredient that would serve as a protectant. Berube and Berdick (Ref. 11) have defined "use thickness" as a practical measure of protectant effect against transepidermal

water loss, as opposed to an earlier work (Ref. 10) that provided a basis for the occlusive thickness of an ingredient necessary to provide zero transepidermal water loss. A minimum of 50 percent (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. This quantity of petrolatum, for example, when spread uniformly on an area 36 cm^2 (an area 2⅓ inches by 2⅓ inches) provides a layer that is approximately 0.3 mm in thickness. This thickness is approximately twice the "use thickness" which Berube and Berdick (Ref. 11) had demonstrated would be necessary to reduce transepidermal water loss by 50 percent. It has been chosen also because of the tendency of protectants to be removed from the anorectal area and because an adequate "use thickness" relative to tissue moisture loss can be effective only as long as it is a contiguous layer (Ref. 11). One g is adequate to shield the area from further insult. Frequent applications, up to six daily, would compensate for the difficulty of the consumer in achieving uniform application as well as maintaining an occlusive layer of the protectant.

This approach provides a reasonable basis for establishing the minimum quantity of an ingredient that must be present for a product to qualify as a protectant. If it can be shown by the same method (Ref. 10) that an ingredient can achieve the same effect at a lower concentration and is also able to relieve anorectal symptoms as discussed under Testing Guidelines, an exception to the 50 percent requirement should be considered. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I). This qualification does not eliminate the possibility of combining as many as four protectants to fulfill the 50 percent requirement.

Itching is a symptom that may arise from many causes. (See part II. paragraph E.1. above—Itching.) It is commonly associated with abraded or irritated epithelium resulting from an underlying disease or from scratching. Normal skin is unlikely to be associated with itching; consequently, itching can be relieved if abraded or irritated skin can be returned to normal. Protection of the perianal area from air, feces, or other irritants will lead to a diminution of irritation and itching. The Panel concludes that Category I protectants can make claims for relief of itching.

The Panel is unaware of any clinical studies showing the relief of burning, pain, and/or itching in the anorectal area by protectants. However, clinical use of protectants for centuries testifies to their effectiveness. Thus, protectants are generally recognized as effective when they provide an occlusive barrier that protects the anorectal area from further insult. The prevention of water loss may be an important factor even though studies in the anorectal area have not been done.

The limitation of four protectant ingredients provides reasonable latitude in the formulation of combinations. The inclusion of more than four active ingredients from the protectant group would only serve to confuse the consumer by the inference that "more" is "better." The Panel concludes that in view of the generally, chemically inert nature of protectants, interaction is unlikely. There is no evidence that combinations of two, three, or four protectants are any better than one. However, protectant active ingredients may also serve as pharmaceutical aids. In recognition of this dual function, the Panel concludes that the maximum number of protectant active ingredients in a product would be limited to four, based on the data submitted to the Panel that four was the maximum number of protectants currently used in OTC anorectal products (Ref. 13).

References

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(2) Blank, I. H., "Factors Which Influence the Water Content of the Stratum Corneum," *Journal of Investigative Dermatology,* 18:433–440, 1952.

(3) Fisher, L. B. and H. I. Maibach, "The Effect of Occlusive and Semipermeable Dressings on the Cell Kinetics of Normal and Wounded Human Epidermis," *in* "Epidermal Wound Healing," Edited by Maibach, H. I. and D. T. Rovee, Year Book Medical Publishers, Inc., Chicago, IL, p. 113, 1972.

(4) Idson, B., "Dry Skin and Emolliency," *Drug and Cosmetic Industry,* 110:28–29 and 108–110, 1972.

(5) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, p. 988, 1970.

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(7) Grollman, A. and E. F. Grollman, "Pharmacology and Therapeutics," 7th Ed., Lea and Febiger, Philadelphia, PA, p. 701, 1970.

(8) Blank, I. H., "Action of Emollient Creams and Their Additives," *Journal of the American Medical Association,* 164:412–415, 1957.

(9) OTC Volume 120052.

(10) Berube, G. R., M. Messinger and M. Berdick, "Measurement in Vivo of Transepidermal Moisture Loss," *Journal of the Society of Cosmetic Chemists,* 22:361–368, 1971.

(11) Berube, G. R. and M. Berdick, "Transepidermal Water Loss. II. The Significance of the Use Thickness of Topical Substances," *Journal of the Society of Cosmetic Chemists,* 25:397–406, 1974.

(12) Minutes of the OTC Panel on Hemorrhoidal Drug Products, 27th meeting, April 29 and 30, 1977.

(13) OTC Volumes 120001 through 120084.

B. Categorization of Data

1. *Category I conditions under which protectant ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

The Panel has classified the following protectant active ingredients as generally recognized as safe and effective and not misbranded:

Aluminum hydroxide gel (external and intrarectal use)
Calamine (external and intrarectal use)
Cocoa butter (external and intrarectal use)
Cod liver oil (external and intrarectal use)
Glycerin in aqueous solution (external use)
Kaolin (external and intrarectal use)
Lanolin (external and intrarectal use)
Mineral oil (external and intrarectal use)
Shark liver oil (external and intrarectal use)
Starch (external and intrarectal use)
White petrolatum (external and intrarectal use)
Wool alcohols (external and intrarectal use)
Zinc oxide (external and intrarectal use)

a. *Aluminum hydroxide gel (external and intrarectal use).* The Panel concludes that aluminum hydroxide gel is safe and effective as a protectant (adsorbent) in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit when present as a single protectant and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description* This is a suspension of aluminum hydroxide and hydrated oxide containing the equivalent of 3.6 to 4.4 percent of aluminum oxide. The substance may be prepared by a number of methods by which gels with different

physical properties are made (Refs. 1 and 2).

(2) *Safety.* The safety of aluminum hydroxide when used as an oral antacid preparation has been established in the final order for antacid and antiflatulent products generally recognized as safe and effective and not misbranded, as published in the **Federal Register** of June 4, 1974 (39 FR 19874), and therefore, can be assumed to be safe for external or intrarectal use in anorectal products. No reports of toxicity in animals has been reported after oral administration, as discussed in the proposal establishing a monograph for OTC antacid products published in the **Federal Register** of April 5, 1973 (38 FR 8717). In humans, the only adverse effects after oral administration consist of the rare occurrence of intestinal obstruction from masses of the unabsorbed gel, sequestration of phosphate, and interference with absorption of tetracycline and possibly other drugs. Evidence concerning interference with absorption of such drugs as tetracycline and anticholinergics is conflicting as discussed in the April 5, 1973, proposal, and is if little importance insofar as anorectal products are concerned. The drug is poorly absorbed from the gastrointestinal tract when taken by mouth, and doses of 5 to 30 mL up to 12 times daily have been used in humans (Ref. 1). It may be assumed, therefore, that absorption through the anorectal area is of no consequence. Insofar as use in anorectal products is concerned, the Panel has found no evidence of toxicity in animals or humans. Aluminum hydroxide has been used for the treatment of peptic ulcer (Ref. 3). This fact, in conjunction with the established safety as an orally administered drug, leads to the conclusion that it is safe for external or intrarectal use in anorectal products.

(3) *Effectiveness.* Local application of aluminum hydroxide gel has been used for the relief of many skin disease, e.g., weeping eczematous lesions, impetigo, epidermophytosis, and tinea (Ref. 4). In general, response is best with moist lesions associated with itching or inflammation, in which the gel acts as an absorbent (Ref. 1). Aluminum hydroxide gel thickened by the addition of kaolin was found effective in providing relief in moist pruritus ani in 93 of 98 patients (Ref. 5); absorption and inactivation of proteolytic enzymes or other irritants in the anal discharge are postulated by the author as the reasons for improvement. Pruritus ani associated with dry skin was not helped by the gel and, therefore, labeling must specify its use in the anorectal area for moist conditions which produce burning, pain, or itch (Ref. 5). Aluminum hydroxide gel has also been used successfully for relief of itching, burning, and pain due to excoriated skin secondary to ileostomies and colostomies (Refs. 6 and 7). In these studies the gel was thickened with kaolin to produce a combination with better adhesion to the affected area. The affected area should be free of petrolatum or greasy ointments prior to application because these substances will interfere with proper adhesion. After oral administration of a kaolin-aluminum hydroxide gel mixture, the author of another study concluded that the mixture adsorbed fecal bacteria completely (Refs. 7 and 8). The Panel finds that aluminum hydroxide is effective for use either intrarectally or externally in anorectal preparations at the recommended dosages.

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the following specific labeling:

(i) *Indications.* (*a*) "For the temporary relief of itching associated with moist anorectal conditions."

(*b*) "Temporarily protects irritated areas from irritating materials."

(ii) *Warning:* "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."

References

(1) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 50–51, 1973.

(2) "The Merck Index," 8th Ed., Merck and Co., Inc., Rahway, NJ, p. 44, 1968.

(3) Adams, W. L. et al., "Aluminum hydroxide as an Antacid in Peptic Ulcer," *American Journal of Digestive Diseases and Nutrition,* 3:112–120, 1936.

(4) OTC Volume 120006, p. 138.

(5) Friedman, M. H. F., B. F. Haskell and W. J. Snape, "Treatment of Pruritus Ani by Local Applications of Aluminum Hydroxide Gel," *The American Journal of Digestive Diseases,* 15:57–60, 1948.

(6) Friedman, M. H. F., "Aluminum Hydroxide Gel for Erosions in Patients with Bowel Fistulas," *Journal of the American Medical Association,* 131:520–522, 1946.

(7) Spiesman, M. G., "Colloidal-Kaolin and Aluminum-Hydroxide Gel (Kalum) in the Management of Lower-Bowel Conditions," *The Review of Gastroenterology,* 10:191–200, 1943.

(8) OTC Volume 120006, p. 162.

b. *Calamine (external and intrarectal use).* The Panel concludes that 5 to 25 percent calamine per dosage unit (based on the zinc oxide content of calamine) when used as a single protectant is safe and effective for external and intrarectal use as a protectant in OTC anorectal preparations and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Calamine is a pink mixture containing not less than 98 percent zinc oxide, which is white, and 0.5 percent ferrous oxide which is red (Ref. 1). Calamine is an odorless, fine powder that is insoluble in water and nearly completely soluble in mineral acids (Refs. 2, 3, and 4).

(2) *Safety.* The pharmacology of this substance is essentially the same as that of zinc oxide and the substance is, therefore, safe for anorectal use. (See part V. paragraph B.1.m.(2) below—Safety.) The ferrous oxide is a pigment that contributes color but is not an active drug.

(3) *Effectiveness.* Calamine is an effective protectant by virtue of its physical qualities, and its effectiveness is the same as that of zinc oxide (Refs. 1, 2, and 3). (See part V. paragraph B.1.M.(3) below—Effectiveness.) Because of this similarity, the Panel concludes that when zinc oxide and/or calamine are present in an anorectal drug product only one of the two substances shall be identified as an active ingredient. Calculations for protectant content must also reflect the total amount of zinc oxide, but use of both forms of zinc oxide constitutes only one protectant ingredient with respect to the combination policy. (See part II. paragraph K. above—Principles Applicable to Combination Products.)

(4) *Dosage.* Adult external and intrarectal dosage is 5 to 25 percent per dosage unit (based on the zinc oxide content of calamine and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

References

(1) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th ED., The Williams and Wilkins Co., Baltimore, MD, p. 98, 1969.

(2) "The Merck Index," 8th Ed., Merck and Co., Inc., Rahway, NJ, p. 189, 1968.

(3) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 208–209, 1973.

(4) "The United States Pharmacopeia," 19th Rev., The United States Pharmacopoeial Convention, Inc., Rockville, MD, p.60, 1975.

c. *Cocoa butter (external and intrarectal use).* The Panel concludes

that cocoa butter is safe and effective as a protectant in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Cocoa butter is the fat obtained from the roasted seed of *Theobroma cocao.* Chemically it is a mixture of sterin, palmitin, olein, laurin, linolein, and traces of other glycerides. It is a yellowish-white solid with faint, agreeable odor and a bland chocolate-like taste. It is brittle below 25 degrees C. Cocoa butter possesses the remarkable property of maintaining its firmness within a few degrees of body temperature at which it readily melts without passing through an appreciable softening stage (Refs. 1 and 2).

(2) *Safety.* While no reports regarding the safety of cocoa butter in anorectal preparations have been found, the Panel recognizes that its safety has been established by its wide and continuous use in pharmacy and cosmetics (Refs. 1, 2, and 3).

(3) *Effectiveness.* Due to its bland, nonirritating properties, cocoa butter is considered to be an excellent protectant (emollient) for application to abraded or irritated anorectal tissue. In addition, it also acts as a protectant by providing a physical barrier against further contact by possible irritants (Ref. 4).

These properties, combined with the fact that it is considered to be a good vehicle for active drugs, are the reasons for its extensive use in suppositories (Ref. 5).

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

References

(1) "The United States dispensatory," Edited by Osal, A. and R. Pratt, 27th Ed., J. B. Lippincott Co., Philadelphia, PA, p. 1179, 1973.

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(5) Mezey, G., "Der Einfluss Lipophiler Emulgatoren auf die Arzneiabgabe aus mit Kakaobutter Hergestellten Suppositorien," *Pharmazie,* 26:166–169, 1971.

d. *Cod liver oil (external and intrarectal use).* The Panel concludes that cod liver oil is safe and effective as a protectant (emollient) in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement and not to exceed a maximum daily dose of 10,000 International Units (IU) vitamin A and 400 IU vitamin D.

Description. Cod liver oil is the fixed oil, partially destarinated, obtained from fresh livers of *Gadus morrhua Linne* and other species of the Family *Gadidae.* Each gram contains not less than 255 μg (850 IU) of vitamin A and not less than 2.12 μg (85 IU) of vitamin D, the latter principally being activated 7-dehydrocholesterol or vitamin D_3. The glyceride components of the oil are principally of unsaturated acids, including arachidonic, clupanodonic, linoleic, linolenic, oleic, zoomaric, and other acids. The oil also contains cholesterol. Cod liver oil is subject to rancidity, and the vitamin A is easily oxidized (Refs. 1 and 2).

(2) *Safety.* While reliable and adequate scientific data regarding the safety of cod liver oil when applied to the anorectal area are not available, an extensive review of the literature on cod liver oil reveals no adverse affects when applied topically as a protectant (emolient) (Refs. 3 through 10). Because cod liver oil is assayed in terms of its vitamin A and vitamin D content, the Panel considered the applicability of the safety data of these ingredients as discussed elsewhere in this document and noted safe limits of vitamins A and D are not exceeded by the recommended dosage of cod liver oil. (See part VIII. paragraph B.3.e. (2) below—Safety and part VIII. paragraph B.3.f. (2) below—Safety.) The Panel concludes that cod liver oil is safe at the recommended dosage for application as a protectant to the anorectal area.

(3) *Effectiveness.* The Panel concludes that the effectiveness of cod liver oil as a protectant (emollient) is due to its bland and soothing effect associated with its oily nature.

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement and not to exceed 10,000 IU vitamin A and 400 IU vitamin D per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1 below—Category I Labeling.).

References

(1) "The National Formulary," 13th Ed., American Pharmaceutical Association, Washinton, DC, p. 183, 1970.

(2) "The United States Dispensatory," 27th Ed. Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, p. 332, 1973.

(3) Daughtry, D. C., "Cod-Liver Oil Ointment in Surgery. Topical Application," *Surgery,* 37: 510–515, 1945.

(4) Grayzel, H. G., C. B. Heimer and R. W. Grayzel, "The Value of a Cod Liver Oil Ointment and Cod Liver Oil Lotion in the Treatment of Dermatoses," *New York State Journal of Medicine,* 53: 2233–2237, 1953.

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(6) Pettit, R. D., "Palliation of Common Obstetric Discomfort," (Abstract), *American Journal of Obstetrics and Gynecology,* 85: 125, 1963.

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(8) Ungar, H., G. Izak and J. D. Feldman, "Hepatic Changes Following Intrasplenic Injection of Fatty Substances," *American Medical Association Archives of Pathology,* 53:470–482, 1952.

(9) Grayzel, H. G. and S. Schapiro, "Wound Healing with Cod Liver Oil Ointment," *Western Journal of Surgery, Obstetrics and Gynecology* 65:558–566, 1956.

(10) "The United States Dispensatory and Physician's Pharmacology," 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altschule, J. B. Lippincott Co., Philadelphia, PA, p. 314, 1967.

e. *Glycerin in aqueous solution (external use).* The Panel concludes that 20 to 45 percent glycerin in aqueous solution is safe and effective as a protectant in OTC anorectal preparations when used in concentrations of at least 50 percent per dosage unit (200 to 450 mg in water to make 1 g) and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Glycerin is a clear, colorless, syrupy liquid, having a sweet taste. It is miscible with water and alcohol but insoluble in chloroform, ether, and in fixed and volatile oils (Ref. 1).

(2) *Safety.* The Panel concludes that glycerin is safe in OTC anorectal preparations. A review of the literature reveals no reports of adverse reactions or irritation to glycerin when used in anorectal preparations.

Glycerin has been administered orally and intravenously with relative safety (Ref. 2). The LD_{50} after oral administration is about 25 g/kg of body weight (Ref. 3), and 5 or 6 g/kg following intravenous administration (Ref. 4). The exact oral toxic dose of glycerin in humans has not been established. In humans, 100 to 300 g of pure glycerin have caused severe symptoms such as

destruction of red blood cells, reddish discoloration of the urine, and kidney failure, but these symptoms can be prevented and are a function of concentration and route of administration. Humans have been given about 100 g daily for 50 days with no ill effects (Ref. 5). Deichmann (Ref. 5) has concluded from a review of animal studies that toxic doses were the largest by the oral route and that the quantity necessary to produce toxicity varied with the mode of administration. The dose needed with the intraperitoneal route was the lowest, and the dose needed with the subcutaneous route was intermediate in toxicity.

The effects of local application of glycerin have been studies using a variety of methods. The immersion of rat's tails in undiluted glycerin produced no changes in the skin (Ref. 4). Application of undiluted glycerin to the conjunctiva of rabbits, cats, and dogs caused no visible changes (Ref. 4). No visible changes were noted following administration of glycerin to the oral mucous membranes of rats, rabbits, and dogs or of the mucous membranes of the stomach in rabbits and dogs (Ref. 4). However, when applied in the rectum of rats and guinea pigs, glycerin caused an accelerated emptying of the intestinal contents (Ref. 4). Studies regarding the skin irritating properties of natural or synthetic glycerin following application to the shaven rabbit dorsal area, (approximately 30 percent of the body surface) indicated that neither skin irritation nor any other abnormalities resulted from topical application of either synthetic or natural glycerin (Ref. 4). These studies (Ref. 4) suggest that glycerin was not absorbed in sufficient quantities to produce a pharmacologic effect.

According to Deichmann (Ref. 6) and Deichmann and Gerarde (Ref. 7), repeated and extensive applications of gylcerin, alone or in 50 percent aqueous solutions, upon the skin of rabbits and rats caused a mild irritation but did not induce definite or fatal intoxication. It has been reported that undiluted gylcerin absorbs water and is somewhat dehydrating and irritating to mucous membranes and particularly to inflamed or sunburned skin (Ref. 8). Therefore, a lower concentration is necessary for safe use in OTC anorectal preparations. There are no reports of reactions with 45 percent concentrations. Hine et al. (Ref. 3) reported that neither natural nor synthetic gylcerin gave evidence of toxic effects. Therefore, the Panel concludes that aqueous solutions of gylcerin in a 20 to 45 percent concentration are safe.

(3) *Effectiveness.* The dehydrating and osmotic actions and gylcerin have been utilized in preparations for local application to furuncles and other inflammatory processes (Refs. 9 through 12). However, this dehydrating effect is most pronounced when glycerin is used undiluted (Ref. 13). Keratin, as represented by a piece of callus, did not show any decrease in brittleness even when 0.1 mL water was added to 4 mL glycerin after 48 hours of exposure. Water alone reduced brittleness by 25 percent in 1 hour (Ref. 13). At best, the application of glycerin has been shown not to affect the ability of keratin to absorb water (Ref. 14). The significance of these findings related to anorectal use is that undiluted glycerin is not effective as a protectant, whereas a dilution of 20 to 45 percent glycerin in water, applied when the relative humidity of air is 30 percent or less as is often the case in winter, will lose water (Ref. 15) to epidermal tissue, and therefore, acts to soften the skin.

While no evidence of its protectant effect when applied to the anorectal area was found on the basis of its physical properties and frequent use as a protectant on the skin (Refs. 9, 10, 11, 16, 17, and 18), it is the Panel's conclusion that glycerin is effective as a protectant in the anorectal area.

(4) *Dosage.* Adult external dosage is 20 to 45 percent glycerin in aqueous solution when used in concentrations of at least 50 percent per dosage unit (200 to 450 mg in water to make 1 g) and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraphs B.1. below—Category I Labeling.)

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f. *Kaolin (external and intrarectal use).* The Panel concludes that kaolin is safe and effective as a protectant (adsorbent) in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Kaolin is a hydrated aluminum silicate, powdered and freed from gritty particles. It is a clay and occurs as a soft, white, or yellowish white powder (Ref. 1).

(2) *Safety.* There are no specific data regarding the safety of kaolin in the treatment of anorectal disorders; however, it is generally considered safe as a protectant (adsorbent) due to the inert nature of aluminum silicate, which is the primary chemical basis of kaolin (Refs. 2, 3, and 4).

(3) *Effectiveness.* Adequately controlled clinical studies demonstrating the effectiveness alone are not available, but the Panel recognizes the value of kaolin as a topical adsorbent based on its extensive use with aluminum hydroxide (Refs. 5, 6, and 7).

Studies confirm its ability to adsorb some drugs (Refs. 8, 9, and 10). It is also considered that kaoline adsorbs some toxins, bacteria, and viruses and is said to provide a protective coating for the intestinal mucosa (Ref. 2). In addition to adsorbing bacteria and various toxins, it has been suggested kaolin may act to increase the resistance to flow by solidifying the colonic contents (Ref. 3), but this has not been demonstrated, as discussed in the proposal to establish monographs for OTC Laxative, Antidiarrheal, Emetic, and Antiemetic products published in the **Federal Register** of March 21, 1975 (40 FR 12928).

As a protectant in combination with aluminum hydroxide, it has been successfully used in such highly irritated wounds as dermatitis, where there is an associated seepage of moist material (Refs. 5 and 6). These studies also indicate the need for specific labeling identified below. Kaolin may also be used as a pharmaceutical necessity to modify the consistency of anorectal preparations (Refs. 2, 3, and 11).

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the following specific labeling:

(i) *Indications.* (a) "For the temporary relief of itching associated with moist anorectal conditions."

(b) "Temporarily protects irritated areas from irritating materials."

(ii) *Warning.* (a) "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."

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g. *Lanolin (external and intrarectal use).* The Panel concludes that lanolin is safe and effective as a protectant (emollient) in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Lanolin is a mixture of components from sheep sebum (Ref. 1) which include wool fat, waxes, and alcohols, as well as constituent esters, fatty acids, and aliphatic alcohols (Ref. 2). The relative amounts of these constituents vary with species of sheep and environment (Ref. 1) as well as with methods of processing. Concentrated lanolin is customarily mixed with 25 to 30 percent water to produce hydrous wool fat (Ref. 3). This material is widely used in medicine and cosmetics as an emollient base or emulsifier for topically applied products (Ref. 4).

(2) *Safety.* Although the toxicity of lanolin in anorectal products has not been determined, the major safety consideration relates to the allergenicity of this heterogeneous mixture when applied to any skin site (Refs. 5 through 13). Although the primary allergic manifestations to topical lanolin is localized dermatitis, systemic manifestation have also been reported (Ref. 9). The incidence of allergic manifestations to topical lanolin in dermatology clinics has been reported to be 1.04 to 1.7 percent (Refs. 5, 7, 8, and 10), but the incidence in the general population is thought to be lower (Ref. 10). Studies have shown that the wool alcohol fraction is the most allergenic (Refs. 1, 2, and 7) and that acetylation or alkylation of the alcohol fraction eliminates this property (Refs. 2 and 8). While there is at least 1 report of allergy to hydrogenated lanolin, more recent data indicate that allergenicity is not a significant problem (Refs. 14 and 15).

In data presented to the Panel citing studies of the International Contact Dermatitis Research Group, the incidence of lanolin allergy was reported to be extremely low (Ref. 15). Further, the patients who were sensitized to lanolin usually had chronic eczema or leg ulcers. Females were found to be more sensitive to lanolin than males. Six physicians reported no allergic reactions to lanolin when it was applied to the anorectal area. The allergenicity of lanolin appeared to be dose related.

The Panel, therefore, concludes that although lanolin will cause allergic reactions or sensitize same patients, it can be used safely by the major portion of the OTC target population and that a warning for safe use is not necessary.

Systemic toxicity due to absorption of lanolin at the anorectal site has not been determined. When applied topically to rat skin, only a small amount of lanolin is absorbed (Ref. 13); the Panel therefore concludes that there is probably no significant systemic toxicity from lanolin use in anorectal products. With regard to direct skin safety, one report of the absence of histological changes after repeated lanolin applications has been made (Ref. 16). However, because there is a tendency for emollients to cause folliculitis in hairy skin areas or in areas subject to friction or sweating (as in the anorectal area), there is a possibility that lanolin could also produce this effect in some persons. Lanolin has been shown to alter the percutaneous (unbroken skin) absorption of certain compounds (Refs. 17 and 18) so that it can potentially increase or decrease the absorption of active ingredients in anorectal products. The Panel does not deem this effect to diminish the safety of anorectal products with lanolin.

(3) *Effectiveness.* No studies can be found substantiating the use of lanolin in the treatment of anorectal lesions. One study, involving the surface of the forearm, demonstrated the ability of petrolatum to reduce moisture loss (Ref. 19). The Panel concludes that lanolin exhibits much the same properties as petrolatum and, therefore, would have the same type of reduction in moisture loss. However, the Panel concludes that, based on the multitude of dermatologic preparations containing lanolin and the widespread use of lanolin over the centuries, lanolin is effective as a protectant (emollient) (Ref. 20).

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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h. *Mineral oil (external and intrarectal use).* The Panel concludes that mineral oil is safe and effective as a protectant in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Mineral oil is a nonvolatile mixture of hydrocarbons (Ref. 1) which is derived from crude petroleum and contains a suitable stabilizer. It is an odorless, colorless, transparent, oily liquid, insoluble in water and alcohol, but soluble in most volatile oils (Ref. 2). Chemically, it is relatively inert. It does not undergo deterioration and cannot become rancid or irritating (Ref. 3). It is widely used externally as an emollient or vehicular aid in creams and suppositories (Ref. 4).

(2) *Safety.* No reports relating to the toxicity or safety of mineral oil in anorectal preparations were found.

In the crude state the precursors of mineral oil and related petroleum derivative medicinals potentially contain a number of polycyclic aromatic hydrocarbons, some of which are carcinogenic. Any statement as to safety is predicated on the assumption that all manufacturers use adequately refined and tested petroleum derivatives that meet established standards of identity and purity (Refs. 5 and 6).

Mineral hydrocarbons, although physically resembling other organic liquids, are not subject to metabolism and can thus remain on the skin indefinitely unless physically removed. They are not absorbed through the skin but may penetrate into hair follicles and glands (Ref. 3); more specifically, liquids, more rapidly than solid fat, can be demonstrated microscpically in lymph channels (Ref. 3). True fats are oxidized, but mineral fats remain and can produce chronic irritation fibrosis and foliculitis. This phenomenon has been amply demonstrated in the many reports of paraffinomas after injection or installation of mineral oil or paraffin into tissues (Refs. 7, 8, and 9). A more relevant report of this occurrence after use of mineral oil as a lubricant for dilation and curettage is available (Ref. 9), which suggests that repeated application of mineral oil hydrocarbons to fissured anal areas or to raw mucosa could result in a similar problem. However, the Panel concludes that, when used as recommended, mineral oil is safe for use in anorectal products.

(3) *Effectiveness.* No studies were found relative to the topical effectiveness of this agent in anorectal disease. However, by extrapolation from use on other parts of the body and by virtue of its physical properties, the Panel concludes that mineral oil is effective as a protectant. A layer of mineral oil is less effective than petrolatum in reducing moisture loss from the outer layer of the skin of the forearm, but it is significantly greater than other materials tested (Ref. 10). This property is also interpreted by the Panel to provide occlusion of the area from external exposure to air, liquids, or other substances within reasonable limits.

Because it is not absorbed, its effect may be prolonged for hours until it is physically removed. The effectiveness of mineral oil and analogous petroleum-derived agents such as lubricants, protective agents, and stable vehicles must be weighed against potential accumulation and persistence until physically removed.

Experimental evidence exists that suggests that mineral oil and related hydrocarbons may definitely influence the absorption of agents with which they are mixed, usually by preventing absorption, but in some cases promoting it (Refs. 11, 12, and 13). Mineral oil is thus capable of rendering an effective combination of agents relatively ineffective.

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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i. *Shark liver oil (external and intrarectal use).* The Panel concludes that shark liver oil is safe and effective as a protectant (emollient) in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement and not to exceed a maximum daily dose of 10,000 IU vitamin A and 400 IU vitamin D.

(1) *Description.* Shark liver oil is an amber to brown oily liquid that contains a mixture of glyceryl esters of fatty acids and other substances, including vitamins A and D. Its content of vitamin A and D may vary but is usually measured in terms of International Units (IU). In the past the oil was assayed biologically and required to have potency of not less than 16,500 IU/g of vitamin A and not less than 40 IU/g of vitamin D (Refs. 1, 2, and 3). Currently, there is no official standard for shark liver oil.

(2) *Safety.* A search of the literature reveals no reports of adverse or toxic reactions to shark liver oil or any controlled clinical studies regarding its safety, but there is ample literature in regard to vitamins A and D. There are no data to confirm that vitamins A and D in shark liver oil are not absorbed. Until such data are available, the Panel concludes that a reasonable maximum allowable concentration for safe OTC topical use is 10,000 IU of vitamin A and 400 IU of vitamin D. Because shark liver oil has been used externally without any known reported local or systemic adverse reaction, the Panel concludes that it is safe, when used as directed, as a protectant for anorectal use.

(3) *Effectiveness.* While no studies relative to the effectiveness of shark liver oil as an individaul ingredient in the treatment of anorectal disease were found, fish liver oils can be considered as having generally similar properties (Ref. 4). Therefore, studies and reports on cod liver oil (Ref. 5) provide a basis and support for extrapolation to the effectiveness of shark liver oil. The Panel concludes that shark liver oil is effective as protectant by coating the area to which it is applied. When used as recommended, it relieves mild irritation of the anorectal area due to its soothing and protective effect associated with its oily nature.

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement and not to exceed 10,000 IU vitamin A and 400 IU vitamin D per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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j. *Starch (external and intrarectal use).* The Panel concludes that starch is safe and effective as a protectant (absorbent) in OTC anorectal products in concentrations of at least 50 percent per dosage unit and not be exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Starch is a crystalline polymeric compound involving linear and branch chain structures of amylose and amylopectin which may be derived from corn or rice (Refs. 1 and 2).

(2) *Safety.* Starch is an insoluble substance and chemically inert. In one study the toxic effects of starch following oral intake have been described. Of the various foodstuffs investigated, starch is by far the least toxic (Ref. 3). Starch in the peritoneal cavity following surgery has produced granulomas, but no toxicity has been reported from topical use on the skin or in the anorectal area. Considering the wide-spread use of starch as a food, the Panel considers these adverse reports as not applicable to OTC anorectal products.

(3) *Effectiveness.* Starch acts by preventing friction and/or by absorbing moisture (Refs. 4 and 5). Talcum is often used in baby formulations (Ref. 5). The Panel concludes that the physical properties of starch are sufficiently similar to talcum so that starch could replace talcum in some baby formulations. The Panel concludes that starch is effective as a protectant to cover the anorectal area and may relieve symptoms of burning, pain, or itch associated with mild irritation (Ref. 6). Because moistened starch can support bacterial growth, it should be washed off before reapplication.

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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k. *White petrolatum (external and intrarectal use).* The Panel concludes that white petrolatum is safe and effective as a protectant (emollient) in OTC anorectal preparations in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Petrolatum (white petrolatum) is a purified mixture of semisolid hydrocarbons obtained from petroleum. A suitable stabilizer may be present. It is a yellowish to light amber unctuous mass. When petrolatum is

treated to remove color, the product is white or faintly yellowish and is officially recognized as white petrolatum (Ref. 1). The uses of white petrolatum are similar to those of petrolatum, but the former is usually preferred over the latter when an ointment of light color is desired.

(2) *Safety.* The safety of petrolatum has been established by its continuous use for almost a century in pharmacy and cosmetics. Also, petrolatum has been prescribed for many decades as a base for anorectal medications.

Some questions have been raised regarding the safety of prolonged and repeated contact of petrolatum with the skin. These questions involve allergenic and carcinogenic potential. The Panel has reviewed the data and concludes that, when petrolatum did not meet the standards as set forth in the official compendia, impurities were the cause of these safety problems (Refs. 2, 3, and 4). When purified grades were investigated by feeding studies on rats and implantation studies on mice, petrolatum was found to be nontoxic, noncarcinogenic, and innocuous in character (Refs. 2, 3, and 4). An unpublished study involving a total of 54 human subjects utilizing a repeated insult patch test procedure indicated that there was essentially no irritation or reaction (Ref. 5). On the basis of the evidence available, the Panel concludes that petrolatum of the purity and quality as set forth in the official compendia (Ref. 1) is safe for application to the anorectal region when used in the recommended dosage. The ability of petrolatum to provide an optimal occlusive surface serves as a model against which other ingredients can be measured as shown by Berube, Messinger, and Berdick (Ref. 6).

(3) *Effectiveness.* Petrolatum applied topically is widely recognized and accepted as a protectant (emollient). Its desirable physical properties and innocuous nature are factors promoting its use as a physical barrier. In the judgment of the Panel, petrolatum serves to reduce further effects of irritants on the affected anorectal area and may relieve burning, pain, or itch produced by these irritants.

The technique of evaluating protectants has been demonstrated utilizing the ability of specific dyes to penetrate a film of ointment which confirms that irritants can be prevented from reaching the epidermis (Ref. 7). Measurement of the actual protection of normal skin surface against contact with water by various ointments showed that white petrolatum was the most effective protectant in 25 of 32 tests (Ref. 8).

(4) *Dosage.* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below-Category I Labeling.

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1. *Wool alcohols (external and intrarectal use).* The Panel concludes that 4 to 7 percent wool alcohols per dosage unit not to exceed six applications per 24 hours or after each bowel movement effective as protectants (emollients) in OTC anorectal preparations are safe.

(1) *Description.* Wool alcohols are constituents of lanolin, which is obtained from sheep sebum (Refs. 1 and 2), and consist of a mixture of aliphatic alcohols (Ref. 2). Wool alcohols can be used as protectants (emollients) or as a pharmaceutical necessity for various pharmaceutical formulations.

(2) *Safety.* The systemic toxicity of wool alcohols administered by any route is not known but is presumed to be low. (See part V. paragraph B.1.g.(2) above—Safety.) Wool alcohols do cause allergic reactions and are believed to be the cause in most cases of lanolin allergy (Refs. 1 and 3). The percentages of wool alcohols that are safe and effective shall not exceed the 4 to 7 percent occurring naturally in lanolin (Res. 4, 5, and 6). The incidence of such allergy to lanolin is questionable (Refs. 3, 7, 8, and 9), but more recent data indicate that allergencity is not a problem among the general population (Ref. 10) using topical preparations according to the recommended dosage. Reportedly, acetylation of wool alcohols decreases allergencity (Refs. 3 and 9), and such treatment should be considered if wool alcohols are separated from lanolin before they are incorporated into OTC drug products.

(3) *Effectiveness.* Wool alcohols are similar in pharmacologic effect to lanolin. The Panel concludes that wool alcohols are effective as protectants (emollients) (Ref. 11) at the 4 to 7 percent concentration naturally occurring in lanolin. (See part V. paragraph B.1.g.(3) above—Effectiveness.) No studies of effectiveness with regard to anorectal use have been found.

(4) *Dosage.* Adult external and intrarectal dosage is 4 to 7 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I labeling.) In addition, the Panel recommends the following specific warning when the wool alcohols have been added to the final formulation as separate ingredients: "*Caution:* Certain persons can develop allegic reactions to ingredients in this product. If redness, irritation, swelling, pain or other symptoms develop or increase, discontinue use and consult a physician."

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m. *Zinc oxide (external and intrarectal use).* The Panel concludes that 5 to 25 percent zinc oxide per

dosage unit is safe and effective as a protectant for use in OTC anorectal preparations and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Zinc oxide is one of a class of bertholide compounds in which the ratio of zinc to oxygen is not exactly 1:1; a property which results in some chemical instabilities (Ref. 1). It is water insoluble, but it is soluble in weak acids and in the presence of fats and tends to form other zinc compounds (Refs. 1, 2, and 3). It will absorb only very small amounts of water (Ref. 4). It is widely employed in a number of dermatologic conditions as an astringent and protective and is often employed as an ingredient of a basic ointment for incorporation of other drugs (Refs. 1 through 5).

(2) *Safety.* Zinc oxide has long been regarded as a relatively nontoxic substance when used both topically and orally (Refs. 5 and 6). Although the oxide is supposed to be inert and not absorbed, it is not completely chemically stable so that free zinc or zinc ions may be available (Ref. 1). However, no specific data are available. It is probable that even if moderate amounts are absorbed systemically they will not exert deleterious effects because zinc is an essential trace metal with 10 to 15 mg daily a part of a normal diet (Refs. 7, 8, and 9) and there are sufficient metabolic mechanisms to cope with increased zinc on at least a short term basis (Ref. 9).

Acute systemic zinc toxicity is manifested by nausea, vomiting, lethargy, and severe pain (Refs. 6 and 10). Chronic toxicity is manifested by anemia and porotic bone changes (Ref. 11). Zinc toxicity relates primarily to amounts greater than 1 g zinc sulfate (Ref. 12) and does not appear to relate to topical applications of zinc or zinc compounds except possibly, although unlikely, from very long-term use. Further, no reports of a direct irritant effect or allergenic effects of zinc oxide were found. Therefore, the Panel concludes it is safe for use in the anorectal area when used as recommended.

(3) *Effectiveness.* Zinc oxide is widely used by dermatologists as a paste to absorb excess moisture and secretions on acute lesions where there is a tendency for vesiculation, oozing, or crusting (Refs. 13 and 14). The Panel concludes that zinc oxide powder forms a protective coating on inflamed areas, and can be an effective protectant (absorbant) in anorectal therapeutics. A study by Steigleder and Raab (Ref. 15) substantiates a protective effect of skin surface against contact with water afforded by 20 percent zinc oxide in 13 of 20 tests. The Panel concludes that in combination a concentration of 5 to 25 percent zinc oxide per dosage unit is necessary to exert a protectant effect.

(4) *Dosage.* Adult external and intrarectal dosage is 5 to 25 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

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Category I Labeling

The Panel recommends the following Category I labeling for protectant active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indications.* (1) "Forms a protective coating over inflamed tissues which can relieve itching."

(2) "Aids in the relief of itching or anorectal discomfort."

(3) "Temporarily forms a protective coating over inflamed tissues which helps prevent drying of tissues."

(4) "Temporarily protects irritated areas from irritating materials."

(5) "Temporarily relieves anorectal itching."

(6) "temporarily relieves burning."

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

(8) "For the temporary relief of itching associated with hemorrhoids, inflamed hemorrhoidal tissue or other anorectal disorders."

(9) "For the temporary relief of local itching associated with hemorrhoids, inflamed hemorrhoidal tissues, or other anorectal disorders."

(10) "For the temporary relief from itching and discomfort due to hemorrhoids or other anorectal disorders."

(11) "Temporarily provides a bland, soothing coating for relief of anorectal discomforts."

(12) "Temporarily provides lubrication in the anorectal area."

(13) "Temporarily lubricates and protects the inflamed irritated anorectal surface to help make bowel movements less painful."

(14) "Temporarily protects from irritation and abrasion during bowel movement."

(15) "Temporarily helps soften and lubricate dry inflamed perianal skin."

(16) "Temporarily relieves the symptoms of perianal skin irritation, and itching."

(17) "Provides lubrication and may help make bowel movements more comfortable."

2. *Category II conditions under which protectant ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredient

The Panel has classified the following protectant active ingredient as not generally recognized as safe and effective or as misbranded:

Bismuth subnitrate (external and intrarectal use). The Panel concludes that bismuth subnitrate is not safe for

use in OTC anorectal products as a protectant.

(1) *Description.* Bismuth subnitrate, also called bismuth oxynitrate, Spanish white, and bismuth paint, is a white, odorless, slightly hygroscopic, almost tasteless powder (Refs. 1 and 2).

(2) *Safety.* There is little information regarding the safety of bismuth subnitrate in the treatment of anorectal disease but significant data regarding poisoning by its local application and/or ingestion. The absorption of bismuth salts through application to open surfaces has been shown in animal and human studies to cause severe ulceration of oral and pharyngeal mucous membranes as well as necrotic, purplish lesions throughout the intestinal tract (Ref. 3). Subcutaneous injections in dogs have produced the same results. Experiments with certain other salts of bismuth have produced the same changes. Thus the repeated symptoms and lesions found in humans and experimentally produced in animals show these toxic effects are due to metallic bismuth (Ref. 3). The signs and symptoms of bismuth intoxication are stomatitis, ulceration, gingival diphtheritic type lesions, dysphagia, nephritis, nausea, and diarrhea (Refs. 1 and 3).

Though most inorganic nitrates are poorly absorbed from the gastrointestinal tract, nitrites, are well-absorbed (Ref. 1). Bismuth subnitrate is converted to nitrite in the presence of bacteria normally found in the bowel such as *E. coli* (Refs. 1 and 4). Because of this change, the action of nitrates and nitrites, especially on smooth muscles, are frequently indistinguishable and the term "nitrite" historically refers to nitrites and nitrates (Ref. 1). The basic action and most common effect of nitrite is its ability to cause dilatation by relaxing smooth muscles, especially those in the arterioles and capillaries. Its ability to relax blood vessels and other organs is independent of nerve supply (Ref. 1). This results in increased rate of capillary blood flow being more effective in the postarterial lower vascular bed. There is a subsequent fall in blood pressure, and thus nitrites, in doses of 65 mg three times daily, were an early treatment for hypertension. The signs and symptoms of nitrite intoxication are vomiting, convulsions, dizziness, sleepiness, methemoglobinemia, and cardiovascular collapse (Refs. 1, 2, and 3). Methemoglobinemia is a condition in which the oxygen is fixed to the hemoglobin in the red blood cell by oxidizing substances such as nitrites, and therefore, cannot be released in the tissues. Unless treated, it can lead to death due to oxygen starvation of the body tissues.

The use of bismuth subnitrate in current times is rare. Due to its spasmolytic (relaxing) effect on blood vessels, bismuth subnitrate has been used for treatment of angina (chest pain due to decreased oxygen to heart) and for high blood pressure. It has also been used as a protectant (adsorbent) in the treatment of diarrheas, intestinal inflammation, and ulcerations (Ref. 1). Through the conversion of bismuth nitrate to nitrite by the presence of *E. coli* in the intestinal tract, the danger arises of absorption of excess amounts of nitrites leading to toxic effects. In children, this is even more dangerous because *E. coli* organisms are commonly found in the upper as well as the lower gastrointestinal tract. Bismuth subnitrate intoxication presents a classic case of methemoglobinemia (Ref. 3), and its frequency of occurrence in children has led physicians not to prescribe this compound for patients under the age of 15 (Ref. 5). This toxic reaction is less common in adults, but since 1935 at least six cases have been reported (Refs. 1 and 3). Three cases, reported out of emergency rooms, would suggest that this type of intoxication is more common than believed and that the less severe reactions probably go unreported by patients and physicians (Refs. 1 and 3). In these three cases, intoxication followed the use of bismuth subnitrate in the treatment of jejunitis, hypochlorhydric gastritis, and inflammation of the bowel, with a 20 g dose in one case administered over 24 hours (Ref. 5). By instillation of bismuth subnitrate directly into the colon, nitrite methemoglobin is produced quickly. A significant number of cases have been reported of methemoglobinemia, including death, in children following ingestion of drinking water (Ref. 6) and local application of dusting powders (Ref. 1). Methemoglobinemia, headaches, and cardiovascular collapse have been reported in adults. Therefore, this compound cannot be considered safe and its toxic effects should prohibit the use of this compound for OTC drug preparations.

(3) *Effectiveness.* Bismuth salts have been used as a protectant (Refs. 1 through 4). There is no evidence that bismuth subnitrate is more effective than other protectant ingredients which are not associated with a safety problem.

(4) *Evaluation.* The Panel concludes that bismuth toxicity can be caused by bismuth subnitrate. Of greater concern than bismuth toxicity is the possibility of nitrite toxicity due to the conversion of nitrate to nitrite in the presence of bacteria normally found in the colon and rectum. The Panel concludes, due to the rapid absorption of nitrites across mucous membranes, that bismuth subnitrate is not safe for use in OTC anorectal products.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of protectant drug products are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claims to be misleading and unsupported by scientific data:

a. "Promotes wound healing." There is no evidence that wound healing is promoted, i.e., proceeds at more than the normal rate.

b. "For temporary relief of inflammation." Inflammation can occur as a result of perirectal abscess, which would not be relieved by such products. This claim is too broad.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following protectant active ingredients listed below. The Panel believes it reasonable to provide 2 years for the development and review of such data. Marketing

need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed in OTC products:

Bismuth oxide (external and intrarectal use)
Bismuth subcarbonate (external and intrarectal use)
Bismuth subgallate (external and intrarectal use)

a. *Bismuth oxide (external and intrarectal use).* The Panel concludes that bismuth oxide is safe for use as a protectant in OTC anorectal preparations, but there is insufficient evidence to prove effectiveness.

(1) *Description.* Bismuth oxide occurs in nature as the mineral bismite. It is a yellow, ordorless powder that is insoluble in water (Ref. 1).

(2) *Safety.* No untoward effects of bismuth oxide have been reported in the available literature. However, the effects are theoretically similar to those of bismuth subcarbonate because they are nearly equally insoluble in water (Ref. 2). Bismuth subcarbonate is used orally in humans to coat the intestinal mucosa at a minimum dosage of 1 g four times daily. (See part V. paragraph B.3.b.(2) below—Safety.) This dosage is used to establish the upper limit of bismuth permitted anorectal preparations. Though absorption of bismuth subcarbonate has been proven in rabbits, the Panel has concluded that it is safe for short term use in human anorectal products at doses of bismuth salts equivalent to 1 g or less bismuth oxide daily. This upper limit may prevent any bismuth salt from meeting the requirement for a protectant in an anorectal drug product (i.e., at least 50 percent per dosage unit) but the Panel permits as many as three additional protectants to be combined so that any final formulation could easily meet the requirement for protectant if such a claim is made.

The lower limit, 17.5 mg bismuth oxide per dosage unit, is based on the lowest quantity present in any of the data submitted for review and does not, in the opinion of the Panel, present a hazard when used according to recommended dosage.

(3) *Effectiveness.* The local action of bismuth oxide probably is due to a mechanical effect of fine insoluble powder (Ref. 3). The properties theoretically are similar to those of bismuth subcarbonate for which the Panel has not found adequate data to support therapeutic claims (See part V. paragraph B.3.b.(3) below—Effectiveness.)

(4) *Proposed dosage.* Adult external and intrarectal dosage is 17.5 to 166 mg per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* Data to demonstrate effectiveness as a protectant will be required in accordance with the guidelines set forth below for testing protectant ingredients. (See part V. paragraph C. below—Data Required for Evaluation.)

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b. *Bismuth subcarbonate (external and intrarectal use).* The Panel concludes that there is insufficient evidence to prove effectiveness of bismuth subcarbonate for use as a protectant in OTC anorectal preparations, but it is safe for use at the recommended dosage.

(1) *Description.* Bismuth subcarbonate is a white to yellow, odorless, tasteless powder which is stable in air but is slowly affected by light with the production of carbon dioxide and bismuth oxide. It is relatively insoluble in water and alcohol (Ref. 1).

(2) *Safety.* When absorbed in various amounts, bismuth can produce lesions of the kidney, liver, gastrointestinal tract and gums, and clinically can result in renal failure and death (Refs. 2, 3, and 4). Most reported cases of bismuth toxicity have been due to the water soluble bismuth salts such as bismuth ammonium citrate, bismuth tartrate, or bismuth subnitrate, administered either parenterally, orally, or topically (Refs. 4 through 9). However, leasions of the kidney have been noted in many patients who received the less soluble bismuth salts for antisyphilitic therapy (Refs. 10 and 11). Oral daily administration of 107 mg/kg of body weight bismuth subcarbonate in beagle dogs for 2 weeks resulted in bismuth deposits of 6 to 14 parts per million (ppm) in the kidneys, as compared to 35 to 115 ppm after the same dose of bismuth as a soluble salt, although no physiological abnormalities were noted. Therefore, it is probable that some bismuth may be absorbed from this relatively insoluble salt. The LD_{50} of bismuth for rabbits is approximately 200 to 400 mg/kg, although the nephrotoxic dose is 85 mg/kg or less (Ref. 12). Because bismuth tends to accumulate in certain tissues, especially kidney, and is only slowly eliminated (Refs. 11 and 13), exposure should be limited. The Panel concludes that bismuth subcarbonate is safe for short term use in OTC anorectal products at doses equal to bismuth oxide. (See part V. paragraph B.3.a.(2) above—Safety.)

(3) *Effectiveness.* The bismuth salts have been promoted as protectants, but no specific reports support this claim. Bismuth subcarbonate is stated to have protective, absorbent, and antacid properties, but experience suggests that none of these is of any great therapeutic importance (Ref. 14). Similar doubts are expressed elsewhere (Ref. 15). Further, one source suggests the therapeutic effectiveness of bismuth salts is dependent upon its solubility (Ref. 16). If this is true, then effectiveness may be correlated with increased toxicity. The purported healing effect of bismuth subcarbonate on inflamed mucous surfaces and wounds by drying the secretion and forming a protective covering or scab has not been clinically established. The local effect is probably due to the physical properties of a fine insoluble powder (Refs. 17 through 20). Bismuth subcarbonate is listed as a topical protectant in an official compendium (Ref. 1). The basis for claims as a protectant can only be reached by bismuth salts when combined with other protectants. (See part V. paragraph B.3.a.(3) above—Effectiveness.) The Panel concludes that there are insufficient data to support the suggestion that bismuth subcarbonate has any effectiveness as a protectant (absorbent) in anorectal products.

(4) *Proposed dosage.* Adult external and intrarectal dosage is 17.5 to 166 mg per dosage unit and not to exceed the equivalent of 1 g bismuth oxide in 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* Data to demonstrate effectiveness as a protectant will be required in accordance with the guidelines set forth below for testing protectant ingredients. (See part V. paragraph C. below—Data Required for Evaluation.)

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c. *Bismuth subgallate (external and intrarectal use).* The Panel concludes that there is insufficient evidence to prove effectiveness of bismuth subgallate as an ingredient for use in OTC anorectal preparations, but it is safe for use at the recommended dosage.

(1) *Description.* Bismuth subgallate is an alkaline salt composed of 46 to 52 percent elemental bismuth. It is practically insoluble in water, alcohol, and ether, and is stable in air, but slightly affected by light (Ref. 1). It has been promoted as an astringent, protectant, and absorbent, as well as an antibacterial agent, although proof of these properties is not found in the literature. It is also used as a bulk and stiffening agent in many suppository preparations.

(2) *Safety.* There are no known studies of the toxicity in animals or humans of bismuth subgallate as a single ingredient. Although the insoluble bismuth salts are reported to be relatively nontoxic (Ref. 2), the degree of toxicity of bismuth compounds varies with the salt used (Refs. 3 and 4), and no studies of this compound have been reported. Intramuscular injections of 200 mg of the moderately insoluble bismuth subsalicylate has produced proteinuria (Refs. 3 and 5), renal tubular damage, hepatic damage, stomatitis, and even death has been reported with high doses of various bismuth salts (Ref. 6). The LD_{50} for various bismuth compounds and metallic bismuth injected intramuscularly in rabbits is 200 to 400 mg/kg (Ref. 3), and a nephrotoxic dose in rabbits is 85 mg/kg. The maximum concentration at which no renal damage is seen has not been established for any of the bismuth salts. Although the topical application to granulating surfaces of the more soluble bismuth compounds has resulted in a number of cases of bismuth intoxication with some deaths (Ref. 7), the specific tolerance limits for mucous membrane and percutaneous absorption of bismuth subgallate has not been studied. Bismuth, reportedly, can be absorbed from topical sites by phagocytosis (Ref. 7) and may be absorbed as a more soluble salt formed either from reaction at the application site or with other constituents in the preparation (Ref. 8). Because bismuth is retained in the body for extended periods of time (Refs. 4 and 9), in a manner similar to lead, repeated use with any degree of absorption of any solubilized salt may result in accumulation. Therefore, the possibility, that chronic use of topical bismuth subgallate in the anorectal area may result in toxicity, forms the basis for dosage restrictions based on its safety. The Panel sets the upper limit at 166 mg per dosage unit, not to exceed 1 g per 24 hours.

(3) *Effectiveness.* Bismuth subgallate has not been shown to be effective as a therapeutic agent. Although numerous reports attest to the clinical effectiveness of suppositories containing bismuth subgallate (Refs. 10 through 14), these reports are primarily anecdotal and no controlled studies have been reported. Therefore, there is no evidence to confirm that this agent alone is responsible for alleviation of anorectal symptoms or that it has protectant (absorbent) effects. Bismuth subgallate is no longer listed in the standard compendia, and several sources share doubt as to its purported effectiveness (Refs. 11, 15, and 16). However, studies were not found to support either positive or negative proof of its effectiveness, although these studies could be carried out quite easily. The basis for claims as a protectant can only be reached by bismuth salts when combined with other protectants. (See part V. paragraph B.3.a. (3) above—Effectiveness.)

(4) *Proposed dosage.* Adult external and intrarectal dosage is 17.5 to 166 mg per dosage unit and not to exceed 1 g per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for protectant active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(6) *Evaluation.* Data to demonstrate effectiveness as a protectant will be required in accordance with the guidelines set forth below for testing protectant ingredients. (See part V. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the following claims. Additional data are required to support the following protectant claims:

a. "Forms a protective coating which may allow healing to occur."

b. "May allow healing to occur by its protective action."

The evaluaiton of these claims must be aimed at "healing effects" if the ingredient for which the claim is made is a Category I protectant. "Healing" is not part of the evaluation of protectant ingredients. (See part VIII. paragraph C. below—Data Required for Evaluation.)

C. Data Required for Evaluation

The Panel has agreed that the protocols recommended in this document for the studies required to substantiate Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing protectant drugs*—a. *General principles.* (1) Establish prevention of transepidermal water loss, or (2) establish ability of the product, through its application, to prevent substances (e.g. dyes and/or water) from contacting the anorectal tissues.

b. *Selection of patients.* (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

c. *Methods of study.* The details of the methods of study would be in accordance with those used in studies establishing the principles stated above, i.e.:

(1) Transepidermal water loss as studied by Berube, Messinger, and Berdick (Ref. 1). (See part V. paragraph B.1.k. above—White petrolatum (external and intrarectal use.)

(2) Prevention of penetration of dyes (Ref. 2).

(3) Prevention of penetration of water (Ref. 2).

(4) (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

d. *Interpretation of data.* A sufficient number of trials must be performed to provide statistically significant results within 7 days.

e. *Evaluation of study.* The testing described above is intended to establish effectiveness. The safety of protectants at dosage limits specified within this document do not require further testing unless new data indicate the need for reevaluation.

References

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VI. Counterirritants

A. General Discussion

A counterirritant is an agent that produces a local sensation that distracts from the perception of pain, burning, or itching. The perception of these symptoms is distracted and commonly replaced by the perception of warmth, cooling, or tingling sensations. Counterirritants have been used empirically for many centuries (Ref. 1).

Counterirritants in low concentrations are therapeutic. Counterirritants in high concentrations can produce severe irritation and tissue damage. The Panel concludes that the concentrations of Category I counterirritants used in external OTC anorectal preparations are safe and effective and will be discussed in greater detail in the individual ingredient statements.

The Panel concludes that there is no therapeutic rationale for using counterirritants intrarectally because there are no identifiable nerve fibers carrying the sensation of pain in rectal mucosa.

The primary mechanism of counterirritation is due to stimulation of nerve impulses. The skin response may be associated with a feeling of comfort, warmth, cooling, or tingling sensations (Refs. 1, 2, and 3). The afferent nerve impulses from the skin are relayed in the cerebrospinal axis to efferent vasomotor fibers supplying internal organs. Thus, the increased circulation to the skin has its counterpart in deeper integumental structures and in viscera innervated from the same segmental level of the central nervous system. Furthermore, when pain arises from an internal organ, sensory impulses simultaneously coming from the skin as a result of the action of an irritant either alter the character of the visceral sensations or, more probably, occupy the final common pathway to the partial or complete exclusion of the impulses arising from the viscera (Refs. 2 and 3). For example, a sore tooth may cause pain and swelling in the cheek by stimulation of the fifth cranial nerve (Ref. 2). The counterirritant is applied to the skin where pain is experienced, and this simple measure will often bring temporary relief (Ref. 2). The perception of other sensations from application of the counterirritant crowds out perception of the pain (Ref. 2).

It is the opinion of the Panel that the number and variety of subjective factors involving the perception of pain require the establishment of methodology for determining effectiveness of this group of drugs. This will require a subjective double-blinded method. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling, in Category I.)

Drugs are the least useful means available for producing counterirritation. Physical measures are employed much more frequently than are chemical agents. Heat is often an important measure, whether as a hot water bottle, heating pad, moist hot pack, or heat lamp (Ref. 3). The Panel concurs on the importance of heat in the relief of anorectal symptoms and recognizes the usefulness of sitz baths (soaking in warm water) as an ancillary measure.

Although no studies of this counterirritation phenomenon in the anorectal area were found, the Panel concludes that one ingredient, menthol

in aqueous solution, used in anorectal drug products does have this property to a sufficient extent to be useful externally for the temporary relief of pain, burning, and itching when used at the recommended dosages. (See part VI. paragraph B.1. below—Menthol in aqueous solution (external use).)

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B. Categorization of Data

1. *Category I conditions under which counterirritant ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredient

The Panel has classified the following counterirritant active ingredient as generally recognized as safe and effective and not misbranded:

Menthol in aqueous solution (external use). The Panel concludes that 0.25 to 1.0 percent menthol per dosage unit in aqueous solution is safe and effective for external use as a counterirritant in OTC anorectal preparations and not to exceed six applications per 24 hours.

(1) *Description.* Menthol is an alcohol obtained from members of the mint family, mainly *Mentha arvensis.* A synthetic form of menthol can be made from thymol and is composed of several stereoisomers varying in physical and toxicological properties. It is slightly soluble in water, very soluble in alcohol, chloroform, ether, glacial acetic acid, and mineral oil (Refs. 1 and 2).

(2) *Safety.* No studies relevant to safety of menthol for anorectal use were found, although absorption and toxicity after topical application of menthol have been reported. Radioactive menthol applied to dogs' chests did appear in the expired air in significant amounts (Ref. 3). Laryngospasm, dyspnea, and cyanosis resulted after fairly extensive topical application of 1 and 2.7 percent menthol ointments to the trunk and faces of two children (Ref. 4). Two deaths have also been reported from intranasal application of menthol ointments, although whether this represented inhalational toxicity or systemic absorption is not clear (Ref. 4).

Menthol is reportedly capable of irritating nasopharyngeal mucous membranes (Ref. 1), but concentrations and mechanisms for this effect are not clear. Menthol is frequently incorporated into cigarettes (1 to 2 mg/cigarette), suggesting a low toxicity. Menthol's ability to increase inflammation while giving symptomatic relief when used intranasally may be relevant to anorectal use (Ref. 1). Menthol is also capable of producing allergic manifestations, although only two reports have been found (Refs. 5 and 6). It is classified as a monocyclic terpene, and terpenes include many sensitizing agents occuring in plants and spices (Ref. 7). In view of the potential as a sensitizing agent and capacity to evoke allergic manifestation, the Panel recommends an appropriate warning. (See part VI. paragraph B.1. below—Category I Labeling.)

Although the relation between systemic absorption through skin or mucous membranes and absorption after oral ingestion is not known, toxicology for oral absorption will be used as a tentative guideline because toxicity by other routes is not quantified. A fatal oral dose of 2 g in human has been reported (Ref. 8). Ingestion of 50 to 500 mg/kg causes severe abdominal pain, nausea, vomiting, vertigo, ataxia, and coma (Ref. 9). Children are more sensitive to smaller doses (Ref. 1), but OTC anorectal ingredients are not recommended for children under 12 years of age. (See part II. paragraph O. above—Pediatric Dosage.)

The toxic level (2 g for adults) is far above the quantity of menthol used in marketed anorectal preparations. Consequently, the Panel concludes that menthol in aqueous solution is safe as a counterirritant for the temporary relief of pain or itching in concentrations of 0.25 percent to 2.0 percent, which is represented by 5 to 40 mg per dosage unit.

(3) *Effectiveness.* Menthol is absorbed through the skin and is widely used as a counterirritant by virtue of its ability to temporarily stimulate nerves for perception of coolness and depress those for pain (Refs. 1 and 10). It is effective locally in concentrations of 0.25 to 1 percent; although the literature reviewed use concentrations as little as 0.1 percent and as high as 3.5 percent, the data on safety and effectivenes support a more narrow range of 0.25 to 2 percent (Refs. 11 and 12). Because the same nerves carry the sensations of pain and itching, the relief of itching, noted in many clinical reports has been explained (Refs. 1, 10, 13, and 14). Pruritus due to histamine is not relieved either by menthol or any other commonly used antipruritic (Ref. 15). There is no proof, however, that histamine sensitivity is involved in the anorectal area; thus, it is reasonable that menthol is useful in the relief of itching.

The Panel has found no studies on menthol used alone in the anorectal area but concludes from effects and wide use on other areas of the body that menthol is effective externally as a counterirritant for the temporary relief of itching in the anorectal area.

(4) *Dosage.* Adult external dosage is 0.25 to 1.0 percent menthol per dosage unit in aqueous solution and not to exceed six applications per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for counterirritant active ingredients. (See part VI. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling:

(i) "May provide a cooling sensation."

(ii) "Temporarily relieves itching and soothes burning."

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Category I Labeling

The Panel recommends the following Category I labeling for counterirritant active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indications.* (1) "For the temporary relief of itching or pain in the perianal area."

(2) "Can help distract from pain or itch."

(3) "Temporary relief of itch or pain in the perianal area."

b. *Warning: "Caution:* Certain persons can develop allergic reactions to ingredients in this product. If redness, irritation, swelling, pain or other symptoms develop or increase, discontinue use and consult a physician."

2. *Category II conditions under which counterirritant ingredients are not generally recognized as safe and and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

The Panel has classified the following counterirritant active ingredients as not generally recognized as safe and effective or as misbranded:

Camphor (external and intrarectal use)
Hydrastis (external and intrarectal use)
Methol (intrarectal use)
Turpentine oil, rectified (external and intrarectal use)

a. *Camphor (external and intrarectal use).* The Panel concludes that camphor is not safe and effective for external and intrarectal use as a counterirritant in OTC anorectal preparations.

(1) *Description.* Camphor is available as colorless crystals or crystalline mass obtained synthetically or naturally from *Cinnamonum camphora.* It volatilizes slowly, but has a pungent, aromatic taste and penetrating odor. Locally, it acts as a counterirritant producing a mild analgesic effect and a rubefacient effect. Systemically, it stimulates the central nervous system.

(2) *Safety.* Absorption of camphor through mucous membranes occurs rapidly and toxic levels may be reached in several minutes (Ref. 1). A major portion is quickly removed from the blood stream and conjugated by the liver into glucuronic acid after being oxidized to campherol or deposited in lipids where it is highly soluble (Ref. 2). Camphor poisoning, due to accidental ingestion, continues to cause morbidity and mortality, especially in children (Refs. 3, 4, and 5). Symptoms are caused by central nervous system stimulation, and death is due usually to subsequent respiratory failure. The probable lethal dose in humans is 50 to 500 mg/kg (Ref. 6).

Toxicity, when ingested, is well-supported by the literature (Refs. 1 through 11). Although there are no data to support toxicity associated with correct use, i.e., in concentrations of 1.6 to 7.0 percent in OTC preparations for anorectal disease, accidental ingestion continues to be a hazard. As noted recently by a physician, "One must ask whether products with tastes attractive to some children, used to soothe a baby's rash, decongest a nose, or treat a fever blister, should contain convulsive or a possibly fatal dose of a toxic compound in teaspoon quantities" (Refs. 5 and 8).

A recent report on two cases of camphor toxicity included a search of the literature in which 500 cases of camphor poisoning were reported in 1973 (Refs. 5 and 8). One submission to the Panel consisted of a letter that strongly recommended the elimination of camphor from the OTC market. This letter included reports of toxicity (Ref. 7).

Because camphor is absorbed so rapidly across mucous membranes, it is or can be highly toxic (Ref. 2); and, in view of its high lipid solubility and potential for storage in fatty tissues, the Panel concludes that it is not safe for use in OTC anorectal preparations.

(3) *Effectiveness.* Because camphor is effective as a counterirritant to relieve itch on other parts of the body, camphor has been used in medicine for centuries, first in China and subsequently in the western world (Refs. 2 and 3). The inclusion of camphor in OTC anorectal products is based on common usage over the centuries. Applied locally, camphor gives a sense of coolness when rubbed lightly and a sense of warmth with vigorous application. As a counterirritant, it relieves itch because of its effect on skin sensory nerves (Ref. 2). There are no controlled data available to support the effectiveness of camphor in anorectal disorders.

(4) *Evaluation.* When used correctly according to directions and in concentrations of 1.6 to 7.0 percent, there is no recorded evidence of significant morbidity and mortality. Yet the lethal dose is small; 50 to 500 (mg/kg) would probably cause death in a 150-pound man (Ref. 6). The effects of cumulative smaller quantities such as 7 percent of a 2-g dose applied six times daily would provide 840 mg of camphor daily. In view of the lipid solubility and consequent tendency to be deposited in adipose tissue, camphor presents an unacceptable hazard. There are not sufficient data to support the effectiveness of the use of camphor in anorectal disorders. Therefore, the Panel concludes that camphor can not be considered generally safe and effective for OTC anorectal products.

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b. *Hydrastis (external and intrarectal use).* The Panel concludes that hydrastis is not safe or effective for external or intrarectal use as a counterirritant in OTC anorectal preparations.

(1) *Description.* Hydrastis is also known as golden seal, yellow root, orange root, Indian Turmeric, eye root

and eye balm (Refs. 1 and 2). It consists of the dried rhizome and root of *Hydrastis canadensis,* which contains varying amounts of hydrastine alkaloids, berberine, and smaller amounts of canadine (Refs. 1 through 4).

(2) *Safety.* The pharmacological action of hydrastis is mainly due to hydrstine and to a lesser extent from berberine. One mL of a 5 percent solution produces strychnine-like convulsions on the intact frog (Ref. 4). The fluidextract administered parenterally to animals produced little or no effect, unless it was given intravenously when hypotension resulted (Ref. 4). Some doubt remains regarding its uterine action, but all reported results indicate that it produces depression of intestinal smooth muscle (Refs. 3 and 4).

Like hydrastis, the alkaloid hydrastine produces stimulation of the central nervous system when given in toxic doses (Ref. 4). Toxic doses causes exaggerated reflexes and strychnine-like convulsions, followed by paralysis and death from respiratory failure (Refs. 4 and 5). Evidence, though somewhat contradictory, suggests that its predominant action on the heart is that of a depressant. Like hydrastine probably produces depression of intestineal smooth muscle (Refs. 3 and 4). The Panel concludes that a 2-g dose of ointment currently containing this ingredient (Ref. 6) provides an unidentified quantity of hydrastis which makes it unsafe for OTC use.

Berberine, unlike hydrastine, has a depressant action on the central nervoud system, as manifested by respiratory depression (Ref. 7). Toxic doses depress the heart, relax blood vessels, depress respiration, and stimulate smooth muscle in the intestine, bronchi, and possibly the uterus (Ref. 3). It is also capable of producting local anesthesia with untoward side reactions (Ref. 8). Gleason et al. (Ref. 3) reports that there is a difference in opinion as to the toxicity of berberine and gives it a toxicity rating ranging from 2 (5 to 15 g/kg) to 5 (5 to 50 mg/kg). The Panel concludes that a 2-g dose of ointment currently containing this ingredient (Ref. 6) provides an unidentified quantity of berberine which makes it unsafe for OTC use.

No data regarding the safety of hydrastis after application to the anorectal area is available. Due to the possibility of absorption of some of the active constituents of hydrastis when applied to the anorectal area, the Panel concludes that hydrastis is not safe for use in OTC anorectal preparations.

(3) *Effectiveness.* Hydrastis was used by the Cherokee Indians both as a pigment and a medicine (Ref. 5). In medicine, the clinical use of hydrastis is based largely on empirical observations. It has few, if any, rational indications for use. The drug has been used as a bitter and stomachic, to check internal hemorrhage, and locally in catarrhal conditions, especially of the genitourinary tract. A survey of the early clinical literature reveals about 50 clinical conditions that were purportedly cured or benefited by hydrastis, hydrastine, or berberine (Ref. 4). Unfortunately, none of these are supported by definitive clinical data.

In his review of the literature published in 1950 pertaining to the pharmacology and therapeutics of hydrastis, Shideman (Ref. 4) noted:

(a) Hydrastis appears to have little effect on the central nervous system except in toxic doses, when it produces convulsive effects analogous to those of strychnine. (b) Parenteral administration of the fluidextract has little or no effect unless given intravenously, when hypotension results, probably because of a direct myocardial depressant effect of the drug. (c) Based on the data available, no conclusions may be drawn regarding its uterine activity, but all reports seem to indicate that it produces depression of intestinal smooth muscle.

A more recent review and a search of the current literature reveals no additional data or information supporting the clinical effectiveness of this drug in the treatment of anorectal disorders (Ref. 5).

The Panel concludes that hydrastis is not effective for use in OTC anorectal preparations because no clinical data supporting such use is available.

(4) *Evaluation.* On the basis of available evidence, the Panel concludes that hydrastis when used in anorectal preparations may be absorbed in sufficient amounts to produce toxicity. In medicine, the clinical use of hydrastis is based largely on empirical observations (Ref. 9). No clinical data supporting its use in anorectal preparations are available. The Panel regards claims as to its effectiveness as a counterirritant as irrational. Therefore, the Panel concludes that hydrastis is not safe or effective for OTC use in anorectal preparations as a counterirritant.

References

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c. *Menthol (intrarectal use).* The Panel concludes that menthol is safe but not effective for intrarectal use as a counterirritant in OTC anorectal preparations.

(1) *Description.* (See part VI. paragraph B.1. (1) above—Description.)

(2) *Safety.* If the intrarectal dose is considered to be equivalent to the oral dose, the fatal amount of natural menthol in man is approximately 1 g/kg (Ref. 1). This large amount greatly exceeds the amount delivered in preparations recommended for external use in which the Panel recommends a concentration of 0.25 to 1 percent menthol per dosage unit in aqueous solution. The Panel concludes that the concentration allowed for external use, therefore, would be safe for intrarectal use. (See part VI. paragraph B.1. (2) above—Safety.)

(3) *Effectiveness.* (See part VI. paragraph B.1. (3) above—Effectiveness.) There are no data to suggest effectiveness of menthol intrarectally. The action of counterirritants is dependent upon the presence of afferent nerves carrying pain sensations in the area to which the agent is applied. Because there are no such nerves in the rectum (rectal mucosa), counterirritants are ineffective in this area.

(4) *Evaluation.* The Panel concludes that menthol in concentrations of 0.25 to 1 percent per dosage unit in aqueous solution is safe but not effective for intrarectal use as a counterirritant because there are no pain sensory nerve fibers in rectal mucosa.

Reference

(1) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 697–698, 1973.

d. *Turpentine oil, rectified (external and intrarectal use).* The Panel concludes that turpentine oil, rectified, is not safe or effective as a

counterirritant in OTC anorectal preparations for external or intrarectal use.

(1) *Description.* Oil of turpentine is a volatile oil and is distilled from gum turpentine from species of *Pinus.* It is a thin, colorless liquid having a characteristic odor and taste, both of which intensify and become unpleasant with aging or exposure to air (Ref. 1). Soluble in oils and alcohol, it is insoluble in water (Ref. 1). It has been used as an expectorant and a stimulant; topically, it has been used as a counterirritant.

(2) *Safety.* Inhaled, it causes headache, confusion, respiratory and gastrointestinal distress (Ref. 2). After subcutaneous injection sterile abscesses result (Refs. 1 and 2). Contact with skin in sensitive individuals will cause erythema and itching (Ref. 2). Aspiration will cause chemical pneumonitis (Refs. 1 and 2). Intoxication is associated with pain, colic, nausea, vomiting, diarrhea, delirium, ataxia, and coma (Ref. 1). Painful urination and the abnormal presence of albumin and red blood cells in the urine are found with absorption of toxic doses (Refs. 1 and 2). Injury to the kidneys and to the gastrointestinal tract result from accidential ingestion (Ref. 2). It is readily absorbed from skin, lungs, and the gastrointestinal tract (Ref. 1). Ingestion of 15 mL in children and 150 mL in adults has caused fatal poisoning (Refs. 1 and 2). From information gathered, toxicity is high in accidental ingestion, use of increased amounts or concentration, and in aspiration and inhalation of vapor (Refs. 1 and 2).

3. *Effectiveness.* Turpentine oil, rectified, is used on the skin as a counterirritant. Review of the literature on this compound failed to demonstrate any support for use of this ingredient in the treatment of anorectal disease.

(4) *Evaluation.* The use of turpentine oil, rectified, on inflamed anorectal skin would cause futher destruction of tissue and increased symptoms. Therefore, the Panel concludes that there is no therapeutic rationale for the use of this ingredient in OTC preparations for anorectal disease and that such preparations should be removed from the market.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the counterirritant drug products are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claim to be misleading and unsupported by scientific data.

"Promotes healing." This claim has no basis in connection with counterirritants.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredient

The Panel concludes that the available data are insufficient to permit final classification of the below named counterirritant active ingredient. The Panel believes it reasonable to provide 2 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 2 years, however, the ingredient listed in this category should no longer be marketed in OTC products:

Juniper tar (external and intrarectal use). The Panel concludes that there is insufficient evidence to prove safety and effectiveness of juniper tar as a counterirritant for use in OTC anorectal preparations.

(1) *Description.* Juniper tar, also called oil of cade, is an oil obtained from the destructive distillation of the wood of *Juniperus oxycedrus.* The oil itself is a dark red, viscid, clear liquid with tar-like odor and warm bitter taste. It is composed of various quantities of the sesquiterpene cadinene, various hydrocarbons, phenol, acetic acid, cresol, and derivatives of pyrotechin, including guaiacol, although information on the relative quantities of these substances was not found. Juniper tar is slightly soluble in water and more soluble in ether (Refs. 1 through 5).

(2) *Safety.* No conclusion as to the actual safety of this heterogeneous mixture of materials could be made by the panel. The toxicity of phenol has been described elsewhere in this document and is pertinent because phenol is considered a representative ingredient of juniper tar. (See part IX. paragraph B.2.d. below—Phenol (external and intrarectal use).) Guaiacol (methylcatechol or methoxyphenol) has been given a toxicity rating of "very toxic" with a lethal does of 50 to 500 mg/kg by Gleason et al. (Ref. 5) and is described as slightly less corrosive and less toxic than phenol, but it is noted that percutaneous absorption is hazardous and skin irritation may result (Refs. 5, 6, and 7). Cresol, another constituent also related to phenol, has a spectrum and level of toxicity similar to phenol and guaiacol with the potential of producing local irritant and systemic effects if absorbed (Refs. 5, 6, and 7). The toxicity of other constituents is not known. Thus, the Panel was unable to judge the safety due to lack of information on the relative concentrations of these constituents as well as a lack of information on the safety of the clinical use of this substance.

(3) *Effectiveness.* The Panel concluded that, although by virtue of the presence of several constituents in juniper tar it could be effective as a counterirritant, lack of information as to the relative amounts of potentially useful constituents as well as any clinical information on effectiveness of the tar prevents any rational conclusion. Anecdotal reports and reviews suggest that it has been popular as an irritant for the treatment of various skin disorders, but no clinical data were found to support this (Refs. 1, 2, 5, and 8). Juniper tar has enjoyed long use as an irritant in the treatment of eczematous skin diseases and pruritus and concentrations from 1 to 5 percent (Ref. 2) and in higher concentrations for scalp treatment. It has also been used in the treatment of a variety of other ailments in ancient and present times in other countries (Ref. 8). Further, the decreasing demand for juniper tar may suggest its declining use. Because it is a mixture of substances, its effectiveness will vary with relative amounts of constituents. Therefore, further data on a standard mixture or isolation of the active components would be recommended for proof of effectiveness.

(4) *Proposed dosage.* Adult external and intrarectal dosage is 20 to 100 mg per dosage unit and not to exceed four applications per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for counterirritant active ingredients. (See part VI. paragraph B.1. above—Category I Labeling).

(6) *Evaluation.* Although widely used for centuries in the treatment of a variety of skin diseases, no reports of definitive clinical evaluation of juniper tar in anorectal diseases have been found.

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Category III Labeling

None.

C. Data Required for Evaluation

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

VII. Astringents

A. General Discussion

Astringents are drugs that are applied to the skin or mucous membranes for a local and limited protein coagulant effect (Ref. 1). The word astringent is derived from the Latin "ad stringere" meaning "to draw firmly together."

When used in therapeutic doses or concentrations, astringents lessen mucus and other secretions and assist in the return to normal of local anorectal irritation and inflammation (Ref. 1). The limited coagulation (precipitation) of proteins protects the underlying tissue and produces a decrease in the volume of cells which is readily demonstrated by macroscopic or microscopic measurements (Ref. 1). A simple illustration of this effect is using an astringent as a mouthwash and noting the puckering effect upon the mucous membranes lining the cheeks (Ref. 1). However, the Panel concludes that the decrease in cell volume (implying a reduction in swelling) is not sufficient to warrant a labeling claim for reduction of swelling. (See part VII. paragraph B.2. below—Category II Labeling.)

Astringents are classified into two groups: (1) Mineral astringents, including heavy metals that combine with the albumin of the tissues and form insoluble precipitates, and (2) the vegetable astringents, such as tannic acid (Ref. 2).

Certain metallic ions, such as zinc, have the ability to precipitate protein and are primarily astringent; however, the astringent effects are considered in connection with its other pharmacological properties (Refs. 3 and 4). Metallic astringents are applied directly to inflammatory lesions of the skin or accessible mucous surfaces. The water insoluble substance, zinc oxide, has been used in a number of pastes and ointments or mixed with starch and kaolin and applied as a dusting powder or as calamine lotion (Ref. 1).

Astringents have a low cell penetrability; therefore, astringent action is essentially limited to the surface cells and interstitial spaces of skin and mucous membranes and is accompanied by contraction, wrinkling, and blanching of the tissue due to hardening of the capillary endothelium (Ref. 3). Mucus and/or other secretions may also be reduced, making the affected area drier (Ref. 5). These surface tissue changes, in the opinion of the Panel, can lead to a reduction of itching.

Although the relief of inflammation has been described, the Panel has found no convincing evidence that actual reduction of inflammation occurs following the application of astringents (Ref. 5). There is a theoretical possibility that the precipitation of surface proteins by astringents could increase inflammation. The mechanism of action of astringents cannot be accurately designated based on this concept, but the Panel recognizes the relief of the symptoms of burning, itching, discomfort, and irritation by astringents.

Some astringents have been used therapeutically to stop minor bleeding by precipitating proteins and by causing platelets to disintegrate and release thromboplastin, thus initiating the clotting mechanism (Ref. 6). The Panel concludes, however, that the potential seriousness of any type of anorectal bleeding does not warrant a labeling claim for control of bleeding. In fact, the Panel has recommended a warning on all anorectal products that anorectal bleeding be evaluated by a physician. (See part II. paragraph Q.5. above—Warnings.)

When astringents coagulate (precipitate) surface tissue protein, a thin layer is formed which can serve to protect underlying tissue. This precipitation can also aid in the removal of dead surface tissue from a wound area.

In summary, the Panel concludes that astringents used in the anorectal area provide an additional mechanism for the temporary relief of the symptoms of burning, itching, discomfort, and irritation.

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B. Categorization of Data

1. *Category I conditions under which astringent ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

The Panel has classified the following astringent active ingredients as generally recognized as safe and effective and not misbranded:

Calamine (external and intrarectal use)

Witch hazel water (external use)

Zinc oxide (external and intrarectal use)

a. *Calamine (external and intrarectal use).* The Panel concludes that 5 to 25 percent calamine per dosage unit (based on the zinc oxide content of calamine) is

safe and effective as an astringent in OTC anorectal preparations and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Calamine is a mixture containing not less than 98 percent zinc oxide and 0.5 percent ferrous oxide. The ferrous oxide is a pigment that provides color but is not an active drug. It is a pink, odorless, fine powder that is insoluble in water and nearly completely soluble in mineral acids (Refs. 1 through 3).

(2) *Safety.* The safety of calamine is the same as that of zinc oxide. (See part V. paragraph B.1.m. (2) above—Safety.) Therefore, the Panel concludes that calamine is safe as an astringent in OTC anorectal preparations for external and intrarectal use.

(3) *Effectiveness.* The effectiveness of calamine is the same as that of zinc oxide. (See part VII. paragraph B.1.c. (3) below—Effectiveness.) Therefore, the Panel concludes that calamine is effective as an astringent in OTC anorectal preparations for external and intrarectal use for the temporary relief of burning and itching.

(4) *Dosage.* Adult external and intrarectal dosage is 5 to 25 percent calamine per dosage unit (based on the zinc oxide content of calamine) and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for astringent active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.)

References

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(3) "The Pharmacopeia of the United States of America," 18th Rev., The United States Pharmacopeial Convention, Inc., Rockville, MD, p. 87, 1970.

b. *Witch hazel water (external use).* The Panel concludes that 10 to 50 percent witch hazel water per dosage unit is safe and effective as an astringent for external application in OTC anorectal preparations and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Witch hazel water (hamamelis water) is prepared by macerating a weighed amount of recently cut and partially dried dormant twigs of *Hamamelis virginiana* for about 24 hours in about twice their weight of water; it is then distilled until no more than 850 mL of distillate is obtained from each 100 g. To each 850 mL distillate, 150 mL alcohol is added. Hamamelis water contains 14 to 15 percent alcohol. It is a clear, colorless liquid having a characteristic odor and taste and is neutral or acid to litmus paper (Ref. 1).

Hamamelis water has not been officially recognized in the standard pharmaceutical compendia since 1960 (Ref. 1). For example, hamamelis water may have alcohol added before or after the distillation process using different concentrations of alcohol (45 to 90 percent) (Ref. 2). It contains only a trace of oil (0.01 to 0.02 percent) (Ref. 3). the tannin of hamamelis bark on distillation remains in the residue and is absent from the distilled extract (Refs. 3 through 12).

(2) *Safety.* Aside from the slight stinging sensation, which has been attributed to the alcohol content (Refs. 9 and 13), no other reports of adverse effects to hamamelis water have been found in the available medical literature. However, because hamamelis water contains minute amounts of volatile oil, the possible occurrence of allergic contact dermatitis cannot be discounted (Refs. 3, 12, and 13).

The Panel concludes that hamamelis water can be used safely and that allergic reaction is rare, based on its long and extensive use.

(3) *Effectiveness.* Literature reports have attributed the astringent action of hamamelis water to its tannin content (Refs. 4, 8, 11, 14, and 15). However, it has been documented that no tannin comes over in the distillate (Refs. 10, 13, and 16). It is probable, but not documentd, that the astringent effect is due to the alcohol present in hamamelis water. Assumptions that its effectiveness is due to the small amount (0.01 to 0.02 percent) of volatile oil that has been found in hamamelis water have not been scientifically validated (Ref. 3). One study shows that hamamelis water shortens bleeding time and accelerates blood coagulation in rabbits (Ref. 3), which may be related to the astringency effects of hamamelis water.

The uses of hamamelis water reported in the literature have not been scientifically tested and are based on folklore (Refs. 13 and 17). Its popularity and use by consumers and the medical profession may be attributed to the trace amount of volatile oil which gives it a characteristically pleasant odor (Refs. 16 and 19). According to data submitted by a manufacturer (Ref. 20), hamamelis water is effective in the relief of itching, the discomfort of hemorrhoids, the relief of the symptoms of anorectal and perineal itch, and for postoperative care after hemorrhoidal surgery (Ref. 13). In one subjective study of 105 postpartum patients with episiotomy discomfort, 102 patients experienced a cooling sensation after the use of pads saturated with a solution containing 50 percent hamamelis water (Ref. 13). In the same study of 76 patients who reported itching, 70 of these patients obtained relief. Seventy-five of 81 patients who reporting burning obtained relief. In a similar study, 49 of 50 postpartum patients with episiotomies reported a cooling sensation; 35 of 38 patients reported relief of itching; and 39 of 43 patients reported relief of burning (Ref. 13). Therefore, the Panel concludes that hamamelis water provides temporary relief of itching and burning and is safe and effective for external application. No data have been presented to indicate that hamamelis water is of any value as an astringent for use in intrarectal application.

(4) *Dosage.* Adult external dosage is 10 to 50 percent witch hazel water per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for astringent active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.)

References

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c. *Zinc oxide (external and intrarectal use).* The Panel concludes that 5 to 25 percent zinc oxide per dosage unit is safe and effective as an astringent in OTC anorectal preparations and not to exceed six applications per 24 hours or after each bowel movement.

(1) *Description.* Zinc oxide is one of a class of bertholide compounds where the ratio of zinc to oxygen is not exactly 1:1; a property that results in some chemical instabilities (Ref. 1). It is water insoluble, but it is soluble in weak acids, and in the presence of fats it tends to form other zinc compounds (Refs. 1, 2, and 3). It does no absorb water (Ref. 4). It is widely employed in a number of dermatologic conditions as an astringent and protectant and has been employed as a major ingredient of a basic ointment for incorporation of other drugs (Ref. 5).

(2) *Safety.* Zinc oxide has long been regarded as a relatively nontoxic substance when used either topically or orally (Refs. 5 and 6). Although the oxide is supposed to be inert and not absorbed (Ref. 4), it is not completely chemically stable so that free zinc or zinc ions may be available. However, no specific data are available.

Zinc is an essential trace metal and part of a normal diet in quantities of 10 to 15 mg daily (Refs. 7, 8, and 9). It is probable that even if moderate amounts are absorbed systemically zinc will not exert deleterious effects because there are suffficient metabolic mechanisms to cope with increased zinc on at least a short term basis (Ref. 9).

In amounts greater than 1 g, systemic zinc toxicity is manifested acutely by nausea, vomiting, lethargy, and severe pain (Ref. 6) and chronically by anemia and porotic bone changes (Ref. 10). Toxicity does not appear to relate to topical applications of zinc or zinc compounds except possibly, though unlikely, from very long-term use (Ref. 11). No reports of direct irritant or allergenic effects of zinc oxide were found.

(3) *Effectiveness.* Zinc oxide is widely used in an official preparation, zinc oxide paste, by dermatologists on acute lesions where there is a tendency to vesiculation, oozing, or crusting because the starch in this formulation absorbs excess moisture and secretions.

Zinc oxide is employed in many dermatologic conditions as an astringent. Its astringent properties are attributed to the ability of the salt to coagulate or precipitate proteins temporarily in the injured or inflamed area (Ref. 12). This provides a protective film, but also may promote healing by other mechanisms. This film cannot be formed on intact skin because free proteins are not present on the horny layer (Ref. 12), but the Panel recognizes that anorectal symptoms of burning and itch usually arise from injured or inflamed skin.

A study by Melton and Shelley (Ref. 13) compares the ability of 54 preparations to relieve itch produced on the forearm by the subcutaneous injection of histamine. The preparations containing zinc oxide did not relieve the itch nor did any of the other ingredients tested. However, the authors conclude that the data do not shed any light on the value of these agents in pruritus arising in skin showing abnormal permeability. Topical epinephrine by iontophroesis and in a penetrant ointment blocked the histamine-induced itching.

Zinc oxide is not generally used as a powder for direct application since it would not remain in contact with the affected area or skin. The usual concentration is 5 to 25 percent (Refs. 14 and 15) in some suitable vehicle to achieve adhesion to the site. The Panel concludes that based on the data reviewed, zinc oxide in a concentration of 5 to 25 percent is safe and effective as an astringent in anorectal preparations.

(4) *Dosage.* Adult external and intratectal dosage is 5 to 25 percent zinc oxide per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(5) *Labeling.* The Panel recommends the Category I labeling for astringent active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.)

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Category I Labeling

The Panel recommends the following category I labeling for astringent active ingredients to be generally recognized as safe and effective and not misbranded.

a. *Indications.* (1) "Aids in protecting irritated anorectal areas."

(2) "Temporary relief of irritation."

(3) "Temporary relief of itching."

(4) "Temporary relief of burning."

(5) "Temporarily relieves itching and soothes burning."

(6) "Temporarilyy relieves discomfort."

b. *Warnings.* None.

2. *Category II conditions under which astringent ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredient

The Panel has classified the following astringent active ingredient as not generally recognized as safe and effective or as misbranded:

Tannic acid (external and intrarectal use). The Panel concludes that tannic acid is not safe or effective as an astringent in OTC anoretcal preparations.

(1) *Description.* Tannic acid is an amorphous powder with a glistening or spongy mass, soluble in water and alcohol, and almost insoluble in chloroform and ether. Natural tannic acid is usually obtained from nut galls that are formed by gall flies and that grow in oak trees.

(2) *Safety.* In 1942, Wells, Humphrey, and Coll (Ref. 1) were the first to report the relationship between absorption of tannic acid in appreciable amounts from large burned areas of the body and subsequent severe central lobular hepatic necrosis (destruction of central areas of liver segments). In 1963, McAlister et al. (Ref. 2) reported three fatalities in children from hepatic necrosis believed to be due to the use of tannic acid in barium enema examinations. In November of the same year five deaths were reported from acute liver failure following administration of barium enemas containing tannic acid (Ref. 3). The age range of these patients was 4 months to 79 years of age. The important pathologic findings were those manifesting severe parenchymal liver damage (Ref. 3).

Proponents for the use of tannic acid in the treatment of diarrhea and burns or continued use in barium enema examinations relied on the investigative studies that indicated insignificant levels of tannic acid in plasma after its use. It was only in the late 1960's that it was shown that the inability to detect significant levels of tannic acid in the plasma after its use was due to its rapid hydrolysis into gallic acid (Ref. 4).

Numerous animal studies have shown that tannic acid is toxic to liver (Refs. 5 through 8). Additional studies revealed injury to the kidney (Ref. 9). The route and duration of administration varied from subcutaneous to rectal, from 1 hour to 215 days (Refs. 5 and 6). A study by Korpassy and Kovacs (Ref. 6) confirmed cancer causing activity of tannic acid with subcutaneous administration but was unable to demonstrate liver changes with skin ulcers that were treated with tannic acid.

Several reports of allergic reaction in patients who became sensitized to tannic acid are found (Ref. 10), although this does not appear of as great a concern as the potential for liver and kidney damage.

therapeutically, tannic acid has been used from a 0.25 percent to 20 percent concentration. It is suggested that liver necrosis may be related to repeated topical applications of tannic acid by extrapolating from reports of liver necrosis in burn patients treated with tannic acid (Ref. 1). It is readily absorbed both through injured skin and mucous membranes and is not safe in the treatment of burns.

Unanimous agreement has not been reached concerning the use of tannic acid in barium enemas and in prebarium enema preparation (Refs. 2, 3, and 11 through 14). Tannic acid has been used as a precleansing enema and with barium sulfate as the ingredient of choice for diagnostic radiological study (Refs. 11 and 12). Tannic acid is believed to decrease mucous secretions by its astringent effect, to give greater mucosal detail by adhering to the bowel wall, to give better pre-X-ray cleansing and post-X-ray evacuation by its irritative effect on the bowel (Ref. 3). Equally effective ingredients for replacement of tannic acid have not been found (Refs. 3 and 15) but because of toxicity, most radiologists have stopped using tannic acid cleansing enemas and many have stopped using tannic acid with barium sulfate for diagnostic radiological study. Those who have continued to use it emphasize careful measurement and preparation to keep the concentration at 1.5 percent or less (Refs. 16 and 17).

(3) *Effectiveness.* Pharmacologically, tannic acid precipitates protein and forms insoluble complexes with many heavy metal ions, alkalies, and glycosides. It has little action on intact skin, but when applied to abraded tissue, it precipitates protein (tannate film) which serves as a mechanical protection (Ref. 18). On application to the mucosa of the gastrointestinal tract, it is said to exert the same protein precipitating effect, decreasing the transudate of fluids (Refs. 11, 12, 18, and 19) and secretions from the wall of the gastrointestinal tract (Ref. 18).

The astringent action of tannic acid on abraded or denuded skin and on mucous membranes has been well-documented (Refs. 11 and 12). Because of this characteristic, it has been used for the symptomatic treatment of diarrhea for years, especially in children (Refs. 18 and 20). Tannic acid was used extensively in the treatment of burns from 1925 to 1943 and was felt to be a protective mechanical barrier, preventing or decreasing the loss of fluids from the burned surface and protecting the burned area from infection (Ref. 18) until it became implicated in liver toxicity. Tannic acid in barium enemas is considered to be superior in dilineating early, significant mucosal changes (Ref. 11).

Tannic acid has been used in treating diarrhea and burns, and also in precleansing preparations; mixed with barium sulfate it is used in diagnostic X-ray studies (Ref. 9). It has been recommended for the treatment of acute anal and perianal inflammation, both as an irrigating fluid to clear out irritating substances and as an agent to slow down the continual drainage of the same irritated perianal skin. It has been used as a local application for protein precipitation to protect the irritated skin, providing a mechanical barrier (Refs. 18, 19, and 21).

This panel is concerned only with the review of the safety and effectiveness of tannic acid in OTC anorectal products. There are no data available to suggest or establish the value of tannic acid in the relief of anorectal symptoms. Therefore, the Panel finds that tannic acid is not effective.

(4) *Evaluation.* With the knowledge of its rapid absorption through inflamed skin and rectal mucosa as well as the knowledge of its hepatic and renal toxicity and its suspected carcinogenic properties, the Panel concludes that tannic acid is not safe or effective for use in OTC anorectal products.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of astringent drugs are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claim to be misleading and unsupported by scientific data.

"Reduction of swelling."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* None.

VIII. Wound-Healing Agents

A. General Discussion

Several ingredients contained in OTC anorectal preparations are purported to have as their only apparent mode of action the acceleration of tissue repair or wound healing. In the following discussion, wound healing is used synonymously with tissue repair.

The primary lesions occurring in the anorectal area which potentially would be affected include hemorrhoids, fissures, and disruption of the protective epithelial surface. These disruptions may involve the epithelium, dermis, and other subcutaneous tissues. In the following discussion, inflamed hemorrhoids and hemorrhoidal tissue are considered as wounds, although the epithelium usually remains intact. The swelling that characterizes hemorrhoids and hemorrhoidal tissue is, in some instances, the result of the same inflammatory response involved in the wound-healing process that takes place anywhere in the body. Various factors will affect the rate of healing (Refs. 1 through 8) such as circulation of blood to the affected area, body position (i.e., erect vs. prone), the presence of disease and drugs. Schilling (Ref. 8) observed that it is more important to avoid complications and retardation of wound healing than to accelerate the normal rate of repair.

A claim for healing is currently associated with some anorectal OTC drug products. The Panel has studied the data submitted that are intended to support the claim for relief of anorectal symptoms as a result of wound-healing mechanisms and has concluded that these may account for the claimed therapeutic activity of the ingredients. However, insufficient work has been done to allow the Panel to conclude that ingredients in anorectal products classified as wound-healing (i.e., tissue repair) agents are generally recognized as safe and effective.

Wound healing is the process of returning an injured area to the condition where it is structurally sound and the surface is intact.

The process of wound healing can be divided into three general stages: (1) Cellular infiltration and inflammation; (2) a fibroblastic stage characterized by proliferation of collagen fibers (collagen synthesis) to form a matrix support for the wounds; (3) a maturation phase in which the collagen matrix is mechanically strengthened by formation of collagen cross-linkages (Refs. 1 and 2). Agents affecting wound healing act at one or more of these stages. Most agents promoting experimental wound healing, such as oxygen, ascorbic acid, and vitamin A appear to act primarily to promote collagen synthesis (Ref. 1).

Corticosteroids are used as antiinflammatory agents in various prescription drug products for anorectal disorders such as ulcerative proctitis to promote healing. The mechanism of action of steroids in ulcerative proctitis is complex and not completely understood. But conversely, steroids are known to retard surgical wound healing by inhibition of collagen synthesis in the second stage (Refs. 1 and 4). This inhibition can, in some cases, be reversed by administration of oral doses of vitamin A, which promotes collagen synthesis (Refs. 1, 4, and 8).

However, the effectiveness of OTC anorectal ingredients in clinical symptomatic relief and/or wound healing in anorectal disease has not been proved. No studies have yet conclusively correlated the use of wound-healing agents with anorectal symptom relief, although the Panel concludes that there is theorectical basis for such a relationship.

The pharmacologic category of wound healers is not one which is generally recognized as effective in the OTC market. The Panel is aware that work is currently in progress to study the effectiveness of wound-healing agents. But these agents have not found an established niche in any OTC drug preparations, nor have any such agents even been specifically recognized as useful in OTC treatment of anorectal disorders. When tested in accordance with part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I, wound-healing agents may be found effective and properly labeled for relieving anorectal symptoms. It is theoretically possible that such agents may prove to be effective for wound-healing when tested in accordance with part VIII. paragraph C. below—Data Required for Evaluation.

A claim for promoting healing of anorectal disorders or hemorrhoids has not previously been associated with ingredients in anorectal products that have been studied as wound-healing agents, e.g., live yeast cell derivative, vitamin A, vitamin D, shark liver oil, cod liver oil, peruvian balsam. One submission to the Panel did contain the label claim "promotes healing," but none of the ingredients have ever been classified as wound-healing agents and there are inadequate data to substantiate this claim.

The Panel recognizes that these wound-healing agents have no primary effect on pain, itching, burning, or swelling, but that relief of these

symptoms may follow as a secondary result of wound-healing, although there are insufficient data to establish the claim for relief of pain, burning, itching, or swelling (e.g., hemorrhoids).

However, the Panel further recognizes that, whatever their mechanism, these ingredients may provide symptomatic relief of discomfort of hemorrhoids. If wound-healing agent ingredients can be shown to be effective, by the subjective testing procedure outlined in an earlier section of this document, then they could make the Category I claim that they do relieve symptons of pain, itching, burning, or swelling. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

The Panel has adopted this dual approach because it recognizes that symptomatic relief is the therapeutic goal in OTC treatment of anorectal disorders, and that products that can prove subjective relief of symptons should be generally recognized as effective, even when the mechanism of action has not yet been conclusively elaborated.

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B. Categorization of Data

1. *Category I conditions under which wound-healing agent ingredients are generally recognized as safe and effective and are not misbranded.* None.

2. *Category II conditions under which wound-healing agent ingredients are not generally recognized as safe and effective or are misbranded.* None.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of wound-healing agent drug products are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claims to be misleading and unsupported by scientific data.

a. "Helps shrink swelling of hemorrhoidal tissues caused by inflammation or infection."

b. "Starts right in to gently help reduce the swelling of hemorrhoidal tissues."

c. "Helps shrink swelling of hemorrhoidal tissues caused by inflammation and gives prompt temporary relief in many cases from pain and itching in tissues."

d. "Promptly relieves pain and itching for hours and actually helps shrink swollen inflamed tissues."

e. "Actually helps shrink the swelling of hemorrhoidal tissues caused by inflammation or infection."

f. "Lets skin heal itself."

g. "Actually helps shrink swollen inflamed tissues."

There is no generally recognized class of substances known as wound healing agents in the OTC market. Therefore, any claim that an ingredient is a wound-healing agent must be demonstrated by appropriate testing. (See part VIII. paragraph C. below—Data Required for Evaluation.)

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following wound-healing agent active ingredients listed below. The Panel believes it is reasonable to provide 2 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed in OTC products.

The Panel has taken into account the fact that these products have been available for a number of years without claims for wound healing and without reports of serious health hazards. However because wound-healing agents are not ingredients generally recognized as existing in the OTC marketplace, the Panel has determined that testing must be quite stringent to prove effectiveness.

Cod liver oil (external and intrarectal use)

Live yeast cell derivative (external and intrarectal use)

Peruvian balsam (external and intrarectal use)

Shark liver oil (external and intrarectal use)

Vitamin A (external and intrarectal use)

Vitamin D (external and intrarectal use)

a. *Cod liver oil (external and intrarectal use).* The Panel concludes that there is insufficient evidence to prove safety and effectiveness of cod liver oil as a wound-healing agent for use in OTC anorectal preparations.

(1) *Description.* (See part V. paragraph B.l.d.(1) above—Description.)

(2) *Safety.* A review of the literature reveals no definitive data regarding the safety of cod liver oil as a wound healing agent in the treatment of anorectal disorders. (See part V. paragraph B.l.d.(2) above—Safety.)

(3) *Effectiveness.* The Panel concludes that claims regarding effectiveness of cod liver oil as a wound-healing agent in the treatment of anorectal disorders remain to be established. Several reports indicate that as a tissue stimulant cod liver oil does alter wound healing favorably (Refs. 1 through 9). Its successful clinical applicability as reported by numerous authors (Ref. 7) indicates that cod liver oil is a factor in promoting tissue repair, clinically and experimentally, but it is unclear whether this is due to its protectant or to its wound-healing effects.

Historically, cod liver oil was widely used clinically during the 1930's. Numerous clinical studies (Refs. 5, 7, and 9) were done, but generally were not double-blind controlled studies. Most of these studies were done prior to the era of antibiotic therapy, and the claimed salutary effects of cod liver oil need to be measured against the antibiotic treatment of wounds (Ref. 7).

In treating injuries of the anorectal area, the effects were not reduced in the presence of viable bacteria or other irritants (Ref. 7). Wounds of the mucous membrane reacted equally well. It is believed and reported by some investigators that increased transudation of leukocytes and fluid following application of cod liver oil medication indicates the presence of irritants that enlarge the vascular bed. Thus, excess fluid is released and there is lysis of necrotic tissue as well as decongestion. Moreover, although cod

liver oil dressings or ointments have been advocated to accelerate healing and reduce infection in burns, ulcers, and superficial wounds (Refs. 9 through 20), controlled observations have failed to substantiate claims of their superiority over other oily preparations used as protectants.

The Panel has concluded that a reasonable daily dosage for OTC anorectal products should not exceed the daily allowance of 10,000 IU vitamin A or 400 IU vitamin D.

(4) *Proposed dosage.* Adult external and intrarectal dosage is 200 mg per dosage unit and not to exceed 4.706 g per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for wound-healing agent active ingredients, pending testing for effectiveness. (See part VIII. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* Data to demonstrate effectiveness as a wound-healing agent will be required in accordance with the guidelines set forth below for testing would-healing agent ingredients. (See part VIII. paragraph C. below—Data Required for Evaluation.) In addition, data are required in accordance with the guidelines set forth in part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I in order to be classified as an anorectal active ingredient.

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b. *Live yeast cell derivative (external and intrarectal use).* The Panel concludes that there is insufficient evidence to prove safety and effectiveness of live yeast cell derivative as a wound-healing agent for use in OTC anorectal preparations.

(1) *Description.* Live yeast cell derivative (LYCD) is a very heterogeneous material of varying composition obtained by a series of extractions of the yeast *Saccharomyces cerevisiae.* Analysis of one batch of LYCD containing 3.6 million units/pound revealed the presence of pantothenic acid (2.5 mg/mL), pentose nucleic acid (7 mg/mL), nonglucose sugars and glutamic aspartic acid, alanine, and lysine (94, 11, 36, and 23 mg/mL, respectively) (Ref. 1). LYCD has a molecular weight of less than 5000 (Ref. 1). The origin of this analyzed batch is not clear, but according to literature supplied in one submission, this factor can be derived from yeast as well as other animal tissues (Refs. 2 through 6). The processes involve filtration of particulate cellular material from alcohol-treated, LYCD-containing filtrate. This filtrate may contain two separate activities, one stimulating respiration and another cell growth (Ref. 7), but it also stimulates the enzymes catalase and peroxidase (Ref. 8). LYCD in most instances will stimulate oxygen uptake in a variety of tissues (Refs. 9 and 10), but this effect is variable and not attributable to the pantothenic acid (Ref. 9). A unit of LYCD has been defined as the amount of LYCD as a dry solid which stimulates the oxygen uptake of 1 mg dry weight of rat abdominal skin by 1 percent (Ref. 11). The correlation between oxygen uptake and wound-healing potency has not been established.

(2) *Safety.* No studies of safety of LYCD have been specifically carried out, although no toxicity has been noted when the compound was used in experimental animals (Ref. 10) and no reports of clinical toxicity have been made or noted in the various clinical studies of the commercial product containing LYCD (Ref. 11). The Panel therefore assumes that the compound is safe for limited use (1 week or less), but does not have evidence for safety of long-term use beyond 7 days.

(3) *Effectiveness.* The effectiveness of LYCD in anorectal drug products in final formulation as submitted to the Panel has not been demonstrated in controlled or uncontrolled clinical trials. Of 4 studies (Ref. 11) reviewed by the Panel involving 416 patients, 2 studies (218 patients) were uncontrolled and single-blinded and the other two studies (198 patients) were double-blinded and uncontrolled but tested against a competitive product of unestablished effectiveness. In the latter studies there was no statistically significant difference between the ointments used. The competitive product also contains a wound-healing agent for which effectiveness has not been established. In addition, a minimum of 7 days was required before responses were to be evaluated by the investigators; this condition places the studies beyond the scope of OTC anorectal drug products. Suppositories containing LYCD showed a statistically significant difference over the competitive products but the same conditions prevailed as for the ointments tested in these studies. However, recent studies presented to the Panel suggest that this agent can promote the synthesis of collagen in vitro, as well as the healing of experimental rabbit ear wounds (Ref. 10). Further, because the rabbit ear wounds were contaminated and the wound healing was still greater than control, the Panel has concluded that these data suggest that LYCD could promote healing in the contaminated anorectal area. In various inflammatory

conditions of the anorectal area, the relevance of collagen synthesis is not established but may be involved in some aspects of recovery of the swollen tissue. Appropriate testing to confirm this relationship, when developed, will permit in vitro verification of effectiveness of any ingredient classified as a wound-healing agent.

The effectiveness of LYCD in a very small study (18 patients) utilizing donor wound sites in patients with burns suggests a method for testing and a potential wound-healing effect (Ref. 12). There is not sufficient evidence to show that LYCD temporarily shrinks swollen hemorrhoidal tissue. The Panel is aware through submitted data that 133.2 units LYCD per dosage unit is the concentration currently used in marketed products and recommends that this concentration be considered as the Panel's proposed dosage for LYCD.

(4) *Proposed dosage.* Adult external and intrarectal dosage is 133.2 units per dosage unit and not to exceed six applications per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for wound-healing agent active ingredients, pending testing for effectiveness. (See part VIII. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* LYCD in the concentration reviewed and proposed in this document does not require further safety testing. Effectiveness of LYCD in relieving anorectal symptoms such as burning, pain, itch, or swelling must be demonstrated. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations and Labeling in Category I.) Further, data to demonstrate effectiveness as a wound-healing agent are also required before claims as a wound-healing agent active ingredient can be made. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(7) *Minority opinion proposing that LYCD be considered safe and effective as a wound-healing age.* The majority of the Panel have stated that live yeast cell derivative (LYCD) should be placed in Category III as a wound-healing agent. The minority opinion is reached that protectants and wound-healing agents should be grouped together under the pharmacologic category of wound-healing agents and that LYCD is safe and effective for OTC use.

The majority of the Panel have decided that LYCD is safe but should be in Category III because double-blind studies have not been made in the human anorectal area to prove that it is effective. The minority argues that the evidence produced in many experiments is far more important than any attempt at proof by double-blind studies.

Double-blind trials have been considered by the Panel as one method by which Category III ingredients can be elevated to Category I. However, there are several practical problems that make such a method very difficult and suggest that some other method should be available. These difficulties include the following considerations:

(i) What is the target population on whom the studies are to be done? Should it be composed of the patients who report to surgeons? Obviously such patients have the most severe diseases, many of which could not be expected to be helped by OTC preparations. Should the target population be from a hospital clinic? Here again the patients are likely to have relatively severe diseases because the costs of clinic care are high. The best target population should be composed of those individuals who come to a pharmacist or to an environment in which OTC drugs are sold because this group will include many individuals with anorectal symptoms that can be expected to respond most satisfactorily to OTC preparations.

The difficulties that accompany such a study are immediately apparent—placebo versus tested drug, a migrant population, lack of adequate follow-up, and possibly some medicolegal considerations make such studies difficult or even valueless, despite great effort.

(ii) The spectrum of anorectal diseases treated is so wide that any controlled clinical study will need an exceptionally large number of entries to prevent skewing of the results. For example, if the study group should happen to include a preponderance of patients with pruritus, the tested group should show unusually good results with essentially any application because most ingredients will relieve this symptom. On the other hand, if a large population of patients should have severe anal fissures, the results could be poor because many of these patients eventually will require surgical relief.

(iii) The normal rate of healing is difficult to define. Theoretically, it should be the time required for the relief of symptoms when no therapy other than cleanliness and warm baths are used. Yet it is hard to find an individual who will refuse to apply in addition a soothing ointment in the presence of troubling symptoms.

(iv) Vehicles used in testing in comparison with any active drug usually are protectants and by themselves will allay symptoms. Thus lanolin, petrolatum, zinc oxide, or cocoa butter can be expected to produce relief in a high percentage of patients from symptoms of pruritus and irritation. The effect of the addition of another active ingredient may be extremely difficult to determine in patients in double-blind studies that rely on symptomatic relief; meanwhile, clear proof of the effectiveness of such an active agent could be obtained by other methods.

(v) Adequate models that furnish closely comparable lesions in different patients are essential if double-blind studies are to be done. To procure them is more difficult. Postoperative hemorrhoidectomy patients or patients with episiotomies could serve but it should be noted that their wounds are deeper and more serious than most wounds that are treated by OTC preparations. Comparable lesions of which the only symptoms are subjective can be judged only by subjective responses. It would be far more scientific to use data that can be obtained by observation by independent investigators and that can be quantitated.

(vi) Patients vary widely in their responses to treatment, depending upon individual differences and also upon the health of the individual at the time that the test is made. It therefore is best to test ingredients with and without vehicles in the same patient at the same time. Such tests in the perianal area at the same time are impossible because one combination placed on one side of the anus necessarily will be mixed rather freely with another placed on the opposite side. Hence, double-blind studies that may appear to be feasible may actually introduce many practical difficulties. It therefore seems reasonable to include a second method by which effectiveness can be judged.

This second method can be described as follows. If an ingredient is proved safe and can be proved to be effective in ex vivo tests, in tests on animals, and in areas of the human body other than the anorectum, it can be accepted as an effective agent. Tests of safety of ingredients rely heavily on such data from animals or other methods of administration of drugs, and it seems only logical that effectiveness should be judged in the same way.

It is proposed that, on this basis, LYCD together with protectants can be classed as wound-healing agents.

Effectiveness can be determined in general either by the relief of symptoms or by healing of the underlying disease. Relief of symptoms may be obtained without healing (e.g. as after application of a local anesthetic to abraded skin) but healing of any underlying disease necessarily will be accompanied by

relief of symptoms. An all-inclusive name to describe the diseases of the rectum that have been listed above may be "lesions" or the popular term "wounds."

Thus, healing of anorectal wounds could be measured by sustained symptomatic relief, in contrast to, for example, temporary relief afforded by local anesthetics or counterirritants. Wound healing, however, is much more complex and can be investigated in many ways that are far more scientific.

Normal healing should be defined as that which occurs under natural circumstances without the application of any type of protection or medication. Experience with wounds in all parts of the body has led to the clinical observation that protective materials hasten healing. The application of a plastic covering or the application of ointments that contain protectants and prevent water loss from the skin have proved effective because they permit healing to occur more rapidly than occurs when a wound is untreated (Ref. 13). Skin grafts from the same individual, from cadavers, or from pigs are used widely in the treatment of wounds due to burns (Ref. 14).

Obviously, there must be a quantitative variation in the speed in which these various agents act. Goodson et al. (Ref. 15) have shown that in the rabbit's ear open wounds heal more rapidly after application of LYCD than after application of petrolatum. That some agents are considered to be more powerful than others have been considered by the Panel, and the pharmacologic group of wound-healing agents was suggested; this designation signified a contribution to wound healing that is much more rapid than occurs with a bland protectant such as petrolatum.

Anorectal tissues in diseased states usually manifest either irritation or varying degrees of inflammation. Irritated skin either has lost its superficial layers of keratin or demonstrates cracks that extend through the corium which consists of dense, vascular connective tissue. These changes are dependent upon water loss, which in turn depends chiefly on a thin layer of epithelial cells near the base of the stratum corneum (Ref. 16). Mild degrees of dryness of the skin lead to scaling, and severe dryness to fissures, inflammation, and dilation of subcutaneous vessels (Ref. 16).

Increased water loss from skin therefore can lead to irritation and inflammation and reduced loss to healing. The water loss from normal skin of the human forearm has been compared with that of skin to which various protectants have been added. Thus, the application of petrolatum led to an average reduction of moisture loss of 48 percent, lanolin to a reduced loss of 32 percent, and mineral oil to a reduced loss of 28 percent (Ref. 17).

The difference in the rate of healing of wounds by the application of various agents has not been studied sufficiently to justify a sharp distinction of protectants and wound-healing agents. In the opinion of the miniority group of the Panel they should be placed together in the pharmacologic group of wound-healing agents.

Despite the observations that wound-healing agents such as protectants have been effective, laboratory studies or quantitative comparisons of various agents until recently have been essentially undeveloped. However, it is now possible to accept evidence from much more conclusive studies that have been done in animals, human skin, and excised anorectal tissues that prove the effectiveness of LYCD, rather than simply to rely on the old clinical dictum of relief of symptoms of itching, burning, pain, or irritation, for which all wound-healing agents could qualify.

These recently developed methods have included the following: (a) Evidence that oxygen uptake of tissues is increased by LYCD. Oxygen supply increases healing due to increased differentiation of fibroblasts and increases collagen synthesis. LYCD has been shown to stimulate oxygen consumption of rat skin, human skin, human fibroblasts, rabbit fibroblasts, and human leukocytes (Ref. 18).

The product tested contains 1 percent LYCD, 3 percent shark liver oil, an ointment base of petrolatum, and phenylmercuric nitrate as a preservative. The oxygen uptake of shaved rat skin when incubated with the product with and without LYCD has been determined (Ref. 19). Increased oxygen uptake occurred with the LYCD.

(b) Collagen synthesis is increased by LYCD. In vivo studies of human skin showed an increased rate of conversion of proline to hydroxyproline in the presence of LYCD (Ref. 18). It is known that one of the major components of the healing process of any wound is accumulation of collagen (Ref. 20), and that the formation of hydroxyproline is a measure of collagen synthesis (Ref. 18).

(c) Using wound chambers that were placed in rabbit skin, LYCD increased the accumulation of tissue within these chambers compared with the tissue in the chambers of the controls. This is accepted as another measure of wound healing (Ref. 18).

(d) Specimen of perianal tissue were excised and tested in vitro to determine the rate of conversion of proline to hydroxyproline, or in other words, the rapidity of the formation of collagen. In three experiments comprising anoderm and perianal tissues and rectal mucosa and submucosa, LYCD increased the collagen synthesis by 82.5 percent (Ref. 21).

(e) Evidence that healing of wounds made on rabbit's ears is more rapid after application of LYCD than after application of petrolatum (Ref. 15).

(f) Evidence in preliminary experiments in a few patients indicated that application of LYCD to one of two paired skin donor sites in humans led to more rapid healing than when the vehicle alone was applied (Ref. 22).

Use of paired donor sites that are to be used when skin grafts are taken furnishes an excellent method that can be carefully controlled because two wounds of uniform depth and size in the same patient can be studied simultaneously. Such a method is capable of wide use in determination of the effectiveness of many ingredients.

(vii) The minority opinion concludes that these sophisticated experiments are much more definitive than attempts to carry out double-blind studies on patients with perianal compliants. Such important observations should not be discarded simply because they have not been done in the perianal area. They are much more conclusive than the alternative method which would require essentially subjective responses to the complaints of itching, irritation, and pain.

It would seem appropriate to include protectants as wound-healing agents. For this pharacologic group, temporary relief of the symptoms of itching, irritation, or pain can be accepted as Category I claims. It is the conclusion of the minority of the Panel that LYCD should be placed together with the Category I protectants in the pharmacologic group of wound-healing agents as safe and effective.

However, if a claim is to be made that certain ingredients are far superior to others and a claim for more rapid healing is made, this will require testing in comparison with all other ingredients in the pharmacologic group of protectants before such claims could be established; the methods cited above within this discussion could be used as models.

(viii) *Labeling*—(*a*) *Category I labeling.* "For the temporary relief of itching, pain, burning, or irritation in the perianal area."

(*b*) *Category II labeling.* (*1*) "Shrinks hemorrhoids."

(*2*) "Promotes more rapid healing than other products."

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(22) OTC Volume 120069.

c. *Peruvian balsam (external and intrarectal use).* The Panel concludes that Peruvian balsam is safe for use as a wound-healing agent, but there is insufficient evidence to prove effectiveness for use in OTC anorectal preparations.

(1) *Description.* Peruvian balsam, also called Indian balsam, China oil, and Honduras or Surinam balsam, is a complex mixture consisting of approximately 25 to 50 percent of an oleoresin and from 50 to 65 percent of a volatile oil that is composed of the esters of benzoic and cinnamic acids, as well as vanillin, benzyl banzoate, benzyl cinnamate, nerolidol, farnesol, small amounts of coumarin, and benzyl alcohol (Refs. 1 and 2). It is obtained from the tree *Myroxylon pereirae*, a member of the *P. leguminosae* family that is native to Central America (Refs. 3 and 4).

(2) *Safety.* The Panel concludes, based on quantities used in submitted data, that Peruvian balsam is safe in concentrations of from 1 to 3 percent (Ref. 5) but notes that it can produce significant skin irritation in higher doses and can also produce allergic skin reactions. This agent has been defined as moderately toxic (toxic dose equals 0.5 to 5 g/kg), but it has been ingested and even injected intravenously without acute ill effects (Ref. 6). Taken orally, up to 50 g of benzoic acid, one of its major constituents, will result in only gastric distress (Ref. 7). In humans, cinnamic acid is largely excreted in the urine as benzoic and hippuric acids (Ref. 6).

Volatile oils are irritating to most tissues (Ref. 7). One study of dermatologic preparations on rabbit skin showed 15 percent Peruvian balsam gave irritation, but 10 percent and 5 percent did not; however, all three showed erythema when combined with X-radiation (Ref. 8).

In contrast, there are several reports attesting to the allergenicity of Peruvian balsam, the incidence ranging from 10 to 20 percent in tested patients (Refs. 9 through 12), with a relatively higher incidence in children (Ref. 9). The fractions or the components of the mixture which have caused the allergenicity have not been identified.

(3) *Effectiveness.* The effectiveness of Peruvian balsam as a wound-healing agent has not been established. When incorporated in an ointment base, it has been used to treat indolent ulcers by theoretically stimulating cell proliferation (Ref. 13). The dosage usually employed is 10 percent in an ointment and approximately 3 percent or less in suppositories (Refs. 13, 14, and 15). There are no available studies proving its effectiveness as a wound-healing agent in anorectal disorders. Although the study by Bloom and Lorincz (Ref. 13), which reported healing of chronic lesions after addition of Peruvian balsam and demonstrated an in vitro antibiotic effect, was suggestive, it falls short of any clear interpretation as to the effectiveness of the agent. Other analogous studies were not found, with the exception of one that also reported beneficial effects on skin lesions, but other potential active ingredients were used together with Peruvian balsam (Ref. 16). Because Peruvian balsam varies in its content (Ref. 1), it is conceivable that any demonstrable effectiveness may vary. Effectiveness would seem to be best determined by identification and examination of the individual components.

(4) *Proposed dosage.* Adult external and intrarectal dosage is 20 to 60 mg per dosage unit and not to exceed 360 mg per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for wound-healing agent active ingredients pending testing for effectiveness. (See part VIII. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* Peruvian balsam in the concentration reviewed and proposed in this document does not require further safety testing. Effectiveness of Peruvian balsam in relieving anorectal symptoms such as burning, pain, itch, or swelling must be demonstrated. (See part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.) Further, data to demonstrate effectiveness as a wound-healing agent are required before this ingredient is labeled as a wound-healing agent in anorectal products. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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d. *Shark liver oil (external and intrarectal use).* The Panel concludes that there is insufficient evidence to prove effectiveness of shark liver oil as a wound-healing agent for use in OTC anorectal preparations when used at the recommended dosage.

(1) *Description.* (See part V, paragraph B.1.j.(1) above—Description.)

(2) *Safety.* Corroborative data establishing the safety of shark liver oil as a wound-healing agent in anorectal preparations is not available. Vitamin A, a normal constituent of shark liver oil, in excess would be harmful, producing a connective tissue resorption syndrome (Ref. 1). However, the Panel found in the data submitted for review that the quantity of vitamin A present (Ref. 2), is sufficiently low (1,710 International Units/gram of product) when the shark liver oil is limited to 3 percent and does not present a hazard to the consumer when used according to the recommended dosage. (See part VIII. paragraph B.3.e.(2) below—Safety.) The safety of vitamin D found in shark liver oil in the concentration used in the data submitted lacks verification when used in the external treatment of anorectal disorders. The Panel finds in the data reviewed that the quantity of vitamin D present in the product containing 3 pecent, by weight of shark liver oil, (Ref. 2) is 2.25 IU/g of product and does not present a hazard to the consumer when used according to the recommended dosage. (See part VIII. paragraph B.3.f.(2) below—Safety.)

(3) *Effectiveness.* The effectiveness of shark liver oil as a wound-healing agent in anorectal preparations has not been confirmed by definitive clinical data (Ref. 1). While some wound healing might be attrubuted to the vitamin A content of shark liver oil, there are not definitive data to support this claim (Ref. 3). Likewise, the effect of vitamin D on soft tissued wounds has not been described but is said to be important in states of rickets, vitamin D deficiency, and abnormal calcium balances (See part VIII. pargraph B.3.e.(3) below—Effectiveness and part VIII. paragraph B.3.f.(3) below—Effectiveness.)

(4) *Proposed dosage.* Adult external and intrarectal dosage is 60 mg per dosage unit and not to exceed 240 mg per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for wound-healing agent active ingredients, pending testing for effectiveness. (See part VIII. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* Data demonstrating the safety and effectiveness of shark liver oil as a wound-healing agent will be required. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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e. *Vitamin A (external and intrarectal use).* The Panel concludes that there is insufficient evidence to prove effectiveness of vitamin A as a wound-healing agent for use in OTC anorectal preparations at the recommended dosage.

(1) *Description.* Vitamin A is a suitable form of retinol or vitamin A alcohol. It may consist of retinol or esters of retinol formed from edible fatty acids, principally acetic and palmitic acids. Retinol is a light yellow to red, oily liquid and is unstable in air and light. Pure vitamin A alocohol occurs as yellow prisms or as yellow crystalline esters of acetic and palmitic acids. All naturally occurring forms are water insoluble. Another representative of vitamin A occurring in nature is vitamin A–2. It has only about one-third the biologic activity of vitamin A–1. and has no commercial significance. Commercial preparations of vitamin A are for the most part synthetic retinol esters and have largely replaced natural vitamin A from fish liver oils. Preparations available range from solutions of pure synthetic vitamin A in oil to numerous fish liver oils and concentrates that contain both vitamin A and vitamin D in various proportions. One IU vitamin A is the specific biologic activity of 0.3 μg of the all-trans isomer of retinol (Refs. 1 through 4). The Panel knows of no studies regarding the degree and extent of absorption of vitamin A through the skin or mucous membranes, factors which would influence both it safety and effectiveness.

(2) *Safety.* The acute toxic dose of vitamin A in the adult is in the range of 2,000,000 to 5,000,000 IU. In the infant; the ingestion of doses as low as 75,000 to 300,000 IU can precipitate acute toxic signs (Ref. 5). Hypervitaminosis occurs both in young children and adults receiving more than 100,000 IU vitamin A daily over several months Ref. 6). There is no evidence to indicate that the oral administration of 10,000 IU vitamin A daily is toxic for any age group.

The Panel knows of no clinical evidence to indicate that external application of vitamin A to the skin or mucous membranes is safe. Absorption of vitamin A through the skin when applied in the form of cod liver oil in infants and in rats has been reported (Ref. 7). Similar absorption from the anorectal area may be presumed to occur, and clinical data regarding degree and extent of absorption are needed to evalutate its safety if an OTC anorectal drug product contains more than 1,710 IU/g, which is the level of currently marketed anorectal drug products. When used at the recommended dosage, this level does not present a hazard to the consumer.

(3) *Effectiveness.* The Panel concludes that vitamin A has an effect on wound-healing as demonstrated by in vitro tests and studies in animals. The Panel makes this conclusion on the basis that the effectiveness of vitamin A in promoting experimental wound-healing is apparently due to its ability to promote collagen synthesis (Refs. 8 and 9). This phenomenon has been demonstrated in a number of well-controlled animal experiments (Refs. 10 through 19). However, the Panel wishes to point out that the clinical effectiveness in the anorectal area remains to be demonstrated in clinical trials of vitamin A as a wound-healing agent in various applications of concentration and dosage interval not to exceed the maximum dose of 10,000 IU (3.44 mg) per 24 hours.

The label for a vitamin A preparation must give the form, source (synthetic or natural), and amount of vitamin A per dosage unit, and the recommended daily dosage.

(4) *Proposed dosage.* Adult external and intrarectal dosage is 1,710 IU (0.5 mg) per dosage unit and not to exceed 10,000 IU (3.44 mg) per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for wound-healing agent active ingredients, pending testing for

effectiveness. (See part VIII. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* When present at the recommended dosage, vitamin A is safe for use in anorectal OTC products. The effectiveness of vitamin A as a wound-healing agent for use in OTC anorectal preparations has not been established. While its wound-healing ability has been demonstrated in animal experiments, no data confirming its effectiveness in the human anorectal area is available. The Panel recommends double-blind clinically significant studies to establish the effectiveness of vitamin A as a wound-healing agent in OTC anorectal preparations. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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f. *Vitamin D preparations (ergocalciferol and cholecalciferol) (external and intrarectal use).* The Panel concludes that Vitamin D preparations are safe for use at the recommended dosage but that there is insufficient evidence to prove effectiveness of vitamin D preparations as wound-healing agents for use in OTC anorectal preparations.

(1) *Description.* Two forms of vitamin D are recognized officially—ergocalciferol (vitamin D–2) and cholecalciferol (vitamin D–3). Ergocalciferol and cholecalciferol occur as white, odorless crystals that are soluble in fats and in fat solvents such as ether, alcohol, or chloroform, but insoluble in water. Both forms are stable over long periods of time in oil solution but are quite unstable in the presence of mineral salts. The activity of the two substances is commonly assumed to be equivalent. One mg of each of these vitamins represents 40,000 IU. Because they are assumed to be equivalent, the collective term, vitamin D, will be used in the following discussion (Refs. 1, 2, and 3).

(2) *Safety.* A search of the literature reveals no definitive data regarding the safety of vitamin D as a wound-healing agent in the treatment of anorectal conditions. The Panel wishes to point out that vitamin D has a serious toxic potential. In large doses of 1,000 to 3,000 IU/kg daily of body weight, vitamin D may produce tetany, acute pancreatitis, convulsions, and pitressin resistant diabetes insipidus; death has resulted both in experimental animals and in man due to renal insufficiency (refs. 4 and 5). A high calcium diet potentiates the toxic effect of vitamin D (Refs. 4 and 5). In infants as little as 1,800 IU daily may lead to possible growth inhibition (Ref. 6). Some persons who are apparently hypersensitive to vitamin D may suffer harmful effects even from low doses. Excessive intake of vitamin D during pregnancy may produce in infants a nonfamilial, congenital, supravalvular aortic stenosis, often in association with other signs of hypercalcemia (Ref. 5). Unfortunately, while there is substantial evidence regarding the toxicity of vitamin D when administered orally in large doses (Ref. 7), there are no similar data regarding its external use in the treatment of anorectal disorders. The studies reported in the literature have dealt with vitamin D as one component of a mixture (Ref. 8). While definitive data regarding the topical absorption of vitamin D are not available, such a possibility cannot be discounted. Thus, it is possible that the amount of vitamin D absorbed following topical application when added to that normally provided by diet (e.g., fortified food or beverages) (Ref. 9) or other sources (e.g., oral vitamin D medication) may be sufficient to result in manifestations of vitamin D toxicity. Furthermore, since the body stores vitamin D, the cumulative effects must also be considered. However, the Panel concludes that vitamin D when used in anorectal drug products at the recommended dosage is safe.

(3) *Effectiveness.* The Panel concludes that the effectiveness of vitamin D as a wound-healing agent in treating anorectal disorders has not been corroborated by controlled clinical trials. Liteature reports deal with vitamin D as a component of a mixture. These studies fail to prove conclusively that positive results, particularly in wound healing, can be attributed to the vitamin D content in the preparations used. Its effectiveness in wound healing has been challenged on the grounds that it is ineffective unless bone is involved or there is a vitamin D deficiency. Preparations like shark liver oil and cod liver oil which contain vitamins A and D have a protectant effect that is attributed to their oily nature (Refs. 10 through 15). No definitive clinical data supporting wound-healing effect in these oils as being due to their vitamins A and D content are available. According to data presented to the Panel, no one has ever shown that vitamin D has any effect on soft tissue wounds. There is no satisfactory evidence to indicate benefits from inclusion of vitamin D in preparations for topical use (Ref. 17).

(4) *Proposed dosage.* Adult external and intrarectal dosage is 4.5 IU (0.00011 mg) per dosage unit and not to exceed 27 IU (0.00066 mg) per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for wound-healing agent active ingredients. (See part VIII. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* There are insufficient definitive clinical data establishing the effectiveness of vitamin D at the recommended dosage as a wound-healing agent in the anorectal area and further testing is to be carried out. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(16) Minutes of the OTC Panel on Hemorrhoidal Drug Products, 14th meeting, May 1, 2, and 3, 1975.

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the claims listed below.

Additional data are required to support the following wound-healing agent claims:

a. "May promote healing of injured or irritated skin or mucous membrane."

b. "May help promote tissue repair in the anorectal area."

c. "For the relief of minor irritations in the anorectal area."

d. "Temporarily shrinks swelling of hemorrhoidal tissue caused by inflammation."

C. Data Required for Evaluation

The Panel has agreed that the protocols recommended in the document for the studies required to bring Category III wound-healing agents into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improvements in methodology in the future.

It should be noted that all OTC anorectal products are primarily used for the relief of symptoms associated with anorectal disorders. Therefore, any ingredient must be shown, in clinical double-blind studies, to be able to relieve one or more of the common symptoms of itch, burning, pain, discomfort, or swelling to a statistically significant degree over control. This requirement is true whether the mechanism is known or not because the mechanism of providing relief is often much more difficult to determine; a study to determine mechanism may not always directly relate to clinical symptomatic relief. In some cases, experiments may demonstrate both symptomatic relief and a mechanism such as healing.

To make a claim as a wound-healing agent, it not only must be demonstrated that such an agent provides symptomatic relief of anorectal symptoms but also that it has the capacity to promote wound healing as shown in clinical testing in the anorectal area as described within this section. (See also part II. paragraph L. above—Criteria and Testing Guidelines for Placing Category III Ingredients, Combinations, and Labeling in Category I.)

1. *Principles in the design of an experimental protocol for testing wound-healing agents*—a. *General principles.* Because of the unique nature of the contaminated and traumatized (by bowel movement, toilet tissue, and sometimes clothing) anorectal area, anorectal agents for which the claim of wound healing is desired should ideally be tested in the anorectal area in humans. Ancillary information suggesting a wound-healing action of other sites is helpful, e.g., collagen synthesis, but would only constitute evidence of activity in the anorectal area if it otherwise corresponds to the demonstrated clinical relief of symptoms. For example, if wound healing requires 14 days and symptomatic relief is obtained in one application, another mechanism must be assumed to be operating and any claim for wound healing is not appropriate.

Two kinds of studies can be developed to demonstrate wound healing. Those done in the anorectal area are called anorectal wound-healing studies, and those done elsewhere on the body are referred to as other clinical wound-healing studies. Those studies carried out in the anorectal area can be designed to test symptomatic relief also, although this might require special precautions to prevent bias.

All studies must be carried out with a 7-day end point to make these studies relevant to OTC use. It is conceivable that some agents may be effective over longer periods or require a longer period of time to demonstrate effectiveness, i.e., more than 7 days, but because OTC use primarily involves symptomatic problems, all prolonged effectiveness claims must be approved through the new drug application process and marketed as prescription drugs.

b. *Selection of patients*—(1) *Anorectal wound healing.* Patients with anorectal disease of a nature that allows quantitation by biopsy, photography, or other studies.

(2) *Other clinical wound-healing studies.* Other studies of wound healing may be done in normal human volunteers or in patients with other relatively defined standard wounds such as skin graft, punch biopsies, or the like. These must be, likewise, quantifiable by measurement, photography, or other quantitative methods, and/or clinical grading system.

c. *Methods of study.* The minumum number of visits should be the initial visit and a followup in not more than 7 days.

(1) *Anorectal wound healing.* Because of the extreme variability and difficulty with study in this area, double-blind studies are needed despite the difficulties involved. Studies should be directed specifically to either external or intrarectal use. Patients will be selected at random manner with sequential

statistical analysis to minimize the number of patients needed. The major criterion for selection of patients is the presence of a lesion that has a potential of healing and that is amenable to consistent quantification. More than one method of quantification may be used but must be consistently used in all comparative studies. Certain methods can be suggested and other methods may be acceptable and can be developed in conjunction with the Food and Drug Administration (FDA). For example, use of a fixed focus camera with standardized lighting can allow clinical grading and measurement of lesion. A clinical grading system is also acceptable in a double-blinded study. In some cases biopsy of skin areas may be feasible, although this is less acceptable due to hazards involved and, more importantly, due to the extreme variability possible because of pathological variations of a given wound site. Certain other measurements of epithelization and wound healing, such as use of dyes or degree of blood flow, may be also shown to be useful. These studies can be correlated with clinical symptomatic improvement by patient questionnaires. However, to prevent bias, methods of data collection that prevent communication of results between patient and doctor should be considered. Such communication has certain undesirable features. If the physician is receiving a fee for service from the patient, the patient will not appreciate any barrier in the way of service for which he is paying. Thus, it may be preferable to do parallel studies of symptoms and pathology in which the treating physician is a person other than the person recording the questionnaire. The recorder may be the patient or another neutral person.

(2) *Other clinical wound-healing studies.* Other studies to test the effects of agents on wound healing must be be designed with the use site in mind, i.e., where there is compression (due to sitting), stretching of surface and subcutaneous tissue on a sporadic basis (due to walking, bowel movement), increased moisture, chafing (due to clothing and opposed body surfaces), and lastly, gross contamination by aerobic and/or anaerobic bacteria and yeast. This is opposed to many body wounds that can be maintained at a relative degree of cleanliness, immobilized, and covered consistently or exposed to air. Although the wound-healing process may be similar in both areas, the natural impediments are not and any experimental design germaine to the anorectal area must consider these impediments. Nonetheless, an agent that causes a significant increase in the healing of wounds at other sites, and also relieves anorectal clinical symptoms over a similar time period can be considered an anorectal wound-healing agent.

Several studies potentially can be carried out using measured skin sites such as a punch biopsy in an easily accessible area on relatively normal skin. Skin graft donor sites, as demonstrated in a submission to the Panel (Ref. 1) may also be used as testing sites. These sites are photographable, and more nearly uniform than other test models. Factors that may be specifically assessed, include swelling, size of site, color, discharge, and epithelialization.

d. *Interpretation of data.* Any effect of the wound-healing rate must be of statistical significance within 7 days. Beyond 7 days, effectiveness is questionable for OTC drug products. If the condition does not improve within 7 days or becomes worse, the consumer is instructed to consult a physician.

(1) *Anorectal studies.* A significantly greater degree of healing in an anorectal area, when p is less than 0.05, allows a Category III agent to be classified Category I if it also produced significant symptomatic improvement in the same or other studies.

(2) *Other clinical wound-healing studies.* Interpretation of other studies must be made with care due to marked differences of sites as noted above. The primary criteria include demonstration of statistically significant healing and correlation of time course of healing with that of clinical improvement, i.e., statistically significant evidence of both types of response with the 7-day limit.

Evidence of effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All data submitted must include negative and positive results.

Reference

(1) OTC Volume 120061.

IX. Antiseptics

A. General Discussion

The Panel defines antiseptics as substances that will inhibit the growth and development of microorganisms without necessarily destroying them. The Panel further concludes that this does not imply that only complete inhibition (sterility) is necessary but rather that partial inhibition is satisfactory. Antiseptics usually include a wide variety of agents such an antimicrobials, bacteriostatics, bactericidals, fungistatics, and fungicidals.

The Panel recognizes that many ingredients including soap and water reduce the number of microorganisms (flora) on the skin. The normal skin flora has traditionally been divided into transient and resident flora (Ref. 1). Transient flora are organisms that are not part of the established normal flora and are picked up from the surrounding environment. Transient organisms are removed with relative ease by washing with soap and water (Ref. 1). In contrast, the resident flora is considered to constitute the established population of skin organisms and is more difficult to remove.

Most OTC anorectal drug products contain more than one ingredient and, therefore, may have more than one effect. Some of these products contain substances intended to prevent or counteract infections and are referred to as antiseptics.

The term antimicrobial (antiseptic) refers to activity against microorganisms regardless of their nature, that is, whether they are bacteria, fungi, mycoplasma, rickettsiae, viruses, or animal parasites. The broadest classification of antimicrobial agents is by the nature of their action. "Cidal" agents kill microorganisms, and "static" agents stop microorganisms from multiplying but do not kill them. Thus, the microorganisms may begin to multiply when the static agent is removed from their environment. The nature of microorganisms varies tremendously so there is no one antimicrobial agent that will kill and/or remove all microorganisms. The antimicrobial agents are commonly designated by their most important area of use or intended purpose. Thus, bactericidal agents destroy vegetative bacterial cells but not necessarily bacterial spores. Fungicidal agents are those intended primarily to destroy fungi. Sporicidal agents are those capable of destroying bacterial and fungal spores. Bacteriostatic and fungistatic agents are those capable of inhibiting the growth of bacteria and fungi, respectively. Not only does the nature of the antimicrobial agent determine whether its action is "cidal" or "static," but the concentration of the agent is important. A substance may have a "static" action in high dilution and a "cidal" action in a more concentrated solution (Ref. 2).

Antimicrobial (antiseptic) activity of a drug is usually determined by in vitro testing and is often compared to a standard known as the phenol coefficient, which is the ratio of the killing efficiency of an antimicrobial agent compared to phenol tested under

identical conditions. To document effectiveness, the antiseptic ability of a drug to prevent or counteract infection in the anorectal area must be demonstrated by in vivo testing.

A number of ingredients submitted to the Panel claim antiseptic properties. After a review of the literature and extensive deliberations, the Panel concluded that the maintenance of relative antisepsis in the anorectal area would be ideal for promoting healing by preventing or counteracting infection. However, the likelihood of achieving anorectal antisepsis greater than that obtained by cleansing with soap and water is small due to the frequent anorectal contamination from large numbers of microorganisms present in feces (Ref. 5).

The Panel concludes that the intrarectal application of antiseptic ingredients is scientifically unsound because of the high percent of anaerobic organisms present in the feces. Studies of the importance of anaerobic bacteria in anorectal disease are very few (Refs. 3 and 4). The Panel believes that if in clincial studies claims for antiseptics are made, attention must be paid to these organisms (anaerobes) as well as to the anaerobes that usually have been used in such studies (Refs. 3 and 4).

For anorectal drug products limited to external application, aerobic organisms are more important because anaerobes will not proliferate in the presence of oxygen.

According to the findings of the Advisory Review Panel on OTC Topical Antimicrobial Drug Products as published in the **Federal Register** of September 13, 1974 (39 FR 33107), there has been widespread use of antimicrobials in soap, surgical scrubs, and preoperative preparations based on the view that the reduction of normal flora to as low a level as possible will have a positive effect on the prophylaxis of disease. However, the Panel further concluded that the interrelationship of the concentration, time of action or contact time, the microbial spectrum, and the possible deleterious effects of drastic changes in the normal flora have been largely ignored in the past or have been superficially investigated. The Advisory Review Panel on OTC Hemorrhoidal Drug Products concurs with the above conclusion and further concludes that the prevention or counteracting of infection in the anorectal area has not been established by the data submitted for ingredients with antiseptic claims.

The Panel recognizes the potential usefulness of antiseptic ingredients on other areas of the body, but due to the unique nature of the anorectal area, effectiveness of these agents cannot be extrapolated because only a partial antisepsis could be achieved at best. The practice of good anal hygiene (cleansing with soap and water) is effective in reducing the number of microorganisms in the anorectal area, and therefore can also aid in the healing process. Thus, although useful in concept, the Panel concludes that proof of any significant clinical benefit of claimed antiseptic ingredients must be demonstrated in clinical trials. (See part IX, paragraph C, below—Data Required for Evaluation.)

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B. Categorization of Data

1. *Category I conditions under which antiseptic ingredients are generally recognized as safe and effective and are not misbranded.*

None.

2. *Category II conditions under which antiseptic ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

The Panel has classified the following antiseptic active ingredients as not generally recognized as safe and effective or as misbranded:

Boric acid (external and intrarectal use)
Boroglycerin (external and intrarectal use)
Hydrastis (external and intrarectal use)
Phenol (external and intrarectal use)
Resorcinol (intrarectal use)
Sodium salicylic acid phenolate (external and intrarectal use)

a. *Boric acid (external and intrarectal use).* The Panel concludes that boric acid is not safe and effective as an antiseptic in OTC anorectal preparations.

(1) *Description.* Boric acid occurs as colorless, odorless scales, crystals, or as a white powder. It is stable in air and freely soluble in boiling water, in boiling alcohol, and in glycerin (Ref. 1). Variable amounts of boric acid are used in anorectal preparations (e.g., 50 percent by weight of total active ingredients per suppository, and up to 18 percent in ointments) (Ref. 2).

(2) *Safety.* There are no specific data regarding the safety of boric acid in the treatment of anorectal disorders. However, there is a great deal of information and supportive data regarding its toxicity after local application to skin ulcers or abrasions, and/or ingestion. Boric acid is readily absorbed from the gastrointestinal tract, serous cavities, and abraded skin (Refs. 3, 4, and 5). When ingested orally, boric acid is slowly but completely absorbed and eliminated through the kidney (Ref. 6). The fatal adult oral dose is estimated to be 15 to 20 g but may be much smaller; for infants less than 5 g may be fatal (Refs. 3 through 8). Toxic symptoms and fatal poisoning, especially in infants, following external application on abraded skin of boric acid solutions, ointments, and powders have occurred (Refs. 3, 4, 5, and 7 through 25). A review of the literature on boric acid poisoning by Valdes-Dapena and Arey (Ref. 5) revealed that about one-third of the patients, 53 of 172, had been treated externally. "In 30 of the reported cases, poisoning was due to the application of pure boric acid to the denuded diaper area; 23 of these were fatal and 7 nonfatal" (Ref. 5). According to Ducey and Williams (Ref. 9), a concentration of 5 mg/100 mL blood is a near lethal concentration in an infant, which they calculate can be attained within a few days using 5 percent borated talc dusting powder during diaper changes when dusting is restricted to 100 cm^2 of skin and only 1 percent of the available boric acid is absorbed. However, Johnstone, Basila, and Glaser (Ref. 21) contend that no case of boric acid poisoning has been proven to be the result of any commercially available baby powder containing 5 percent boric acid and conclude from a review of the literature that all of the reported cases of infant mortality attributed to boric acid poisoning have resulted from the injudicious use of boric acid, either from its inadvertent oral administration, intravenous or subcutaneous injection, or from the application of boric acid powder or some homemade preparation containing a high concentration of boric acid to an area of denuded or injured skin.

Anorectal diseases may include inflamed mucosal membranes or abraded skin, which would have a greater ability to absorb boric acid than normal skin (Refs. 3, 5, 7, 8, 16, and 26). The toxic nature of boric acid, as documented by the occurrence of fatal poisonings, particularly in children, has convinced the Panel that it is not safe for use in OTC anorectal preparations.

(3) *Effectiveness.* A review of the literature reveals no clinical data supporting the effectiveness of boric acid in OTC anorectal preparations. While boric acid is claimed to possess weak bacteriostatic and fungistatic activity, it is considered to be of little value as a bactericide (Refs. 6, 7, 8, 10, and 26 through 29). a literature review reveals few controlled studies to support the variety of claims regarding its effectiveness and no definitive data regarding its effectiveness in OTC anorectal preparations. Its therapeutic value is not established, and it has fallen into disrepute because of the occurrence of fatal poisonings, particularly in infants (Refs. 10, 15, 18, 23, 29, 30, and 31).

(4) *Evaluation.* The toxicity of boric acid when applied externally is well documented in the literature. Since anorectal symptoms may be due to inflamed skin and/or mucous membranes that would absorb more boric acid than normal skin, the Panel concludes that boric acid is not safe for anorectal use in OTC anorectal preparations as an antiseptic. Furthermore, there is no evidence in the literature which confirms the effectiveness of boric acid in anorectal products.

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b. *Boroglycerin (external and intrarectal use).* The Panel concludes that boroglycerin is not safe and effective as an antiseptic in OTC anorectal preparations.

(1) *Description.* Boroglycerin (boric acid glycerite) is a viscous, yellowish liquid prepared by the splitting out of three molecules of water from the reaction of equimolar amounts of glycerin and boric acid at 140° to 150° C and contains approximately 50 percent boroglycerin. The boroglycerite form is a compound of indefinite composition (Ref. 1). Its formula is assumed to be $C_3H_5BO_3$. It is soluble in water and its solution is acidic in nature (Ref. 2). Boroglycerin is essentially a soluble preparation of boric acid which, when dissolved in water, hydrolyzes into boric acid and glycerin (Ref. 3).

(2) *Safety.* A search of the literature reveals no information regarding the safety of boroglycerin in OTC anorectal preparations. According to Gleason et al. (Ref. 4), boric acid glycerite is moderately toxic with a probably lethal dose of 0.5 to 5 grams/kilogram (g/kg) in a 70 kilogram (kg) man. Aqueous solutions may also be quite irritating (Ref. 5), especially when applied to injured tissue. Because boric acid glycerite hydrolyzes to boric acid when dissolved in water (Ref. 3), the comments made in evaluating the safety of boric acid are applicable. (See part IX. paragraph B.2.a.(2) above—Safety.) The Panel concludes that the 31 percent weight in weight (w/w) content of boric acid (Ref. 6) in this preparation makes it an equally hazardous preparation and not safe for use in OTC anorectal preparations.

(3) *Effectiveness.* Local application, after dilution with water, is reported to have a dehydrating and antiseptic effect, but there is no evidence to support these claims (Ref. 1). It has been used as a suppository base in the preparation of boroglycerin suppositories (Refs. 1 and 2). Because boric acid glycerite hydrolyzes to boric acid when dissolved in water (Ref. 3), the comments made in evaluating the effectiveness of boric acid are applicable. (See part IX. paragraph B.2.a.(3) above—Effectiveness.) Therefore, the Panel concludes that the effectiveness of boroglycerin in OTC anorectal

preparations is not supported by definitive clinical data.

(4) *Evaluation.* The Panel concludes that due to the content of boric acid in boroglycerin, it is not safe and effective for use in OTC anorectal preparations as an antiseptic. (See part IX. paragraph B.2.a. above—Boric acid (external and intrarectal use).)

References

(1) "Roger's Inorganic Pharmaceutical Chemistry," Edited by Soine, T. O. and C. O. Wilson, 8th Ed., Lea and Febiger, Philadelphia, PA, p. 126, 1967.

(2) Parks, L. M. et al., "Inorganic Chemistry In Pharmacy," J. B. Lippincott Co., Philadelphia, PA, pp. 227–237, 1949.

(3) "Remington's Pharmaceutical Sciences," 13th Ed., Edited by Martin, E. W., Mack Publishing Co., Easton, PA, p. 449, 1965.

(4) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., The Williams and Wilkins Co., Baltimore, MD, p. 25, 1969.

(5) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, Jr., J. B. Lippincott Co., Philadelphia, PA, p. 193, 1955.

(6) "The National Formulary," 10th Ed., American Pharmaceutical Association, Washington, DC, p. 95, 1955.

c. *Hydrastis (external and intrarectal use).* The Panel concludes that hydrastis is not safe or effective for external or intrarectal use as an antiseptic in OTC anorectal preparations.

(1) *Description.* (See part VI. paragraph B.2.b.(1) above—Description.)

(2) *Safety.* (See part VI. paragraph B.2.b.(2) above—Safety.)

(3) *Effectiveness.* The Panel has found no evidence that hydrastis is effective as an antiseptic. (See part VI. paragraph B.2.b.(3) above—Effectiveness.)

(4) *Evaluation.* The Panel concludes that hydrastis is not effective for use in OTC anorectal preparations because no clinical data supporting such use as an antiseptic are available.

d. *Phenol (external and intrarectal use).* The Panel concludes that phenol is not safe as an antiseptic in concentrations of 1.5 percent or greater and is ineffective at this concentration for use in OTC anorectal preparations.

(1) *Description.* Phenol is a colorless, crystalline compound having a characteristic odor. It is soluble to the extent of approximately 6 g/100 g water. It is miscible with alcohol or glycerin. A mixture of liquified phenol and an equal volume of glycerin is miscible with water (Refs. 1, 2, and 3).

(2) *Safety.* The Panel concludes that phenol in concentrations greater than 1.5 percent in aqueous or alcoholic vehicles is not safe. The data supporting this decision may be found in various standard reference tests that document the toxicity of phenol when applied topically to skin or mucous membranes (Refs. 1 through 5).

Deichmann and Keplinger (Ref. 3) demonstrated the ability of the descending rabbit colon to absorb phenol faster than the stomach or ileum. Although 1 g may be fatal to humans and exceptional patients have survived 65 g, 50 percent of all cases reported through 1929 terminated fatally (Ref. 3). One to 5 percent phenol applied as a dressing or compress has caused gangrene (Ref. 3). Five percent in oil when injected to relieve hemorrhoids has caused serious problems including gangrene and liver enlargement (Ref. 6). Phenol also penetrates the sensory nerve endings and exerts a local anesthetic action (Ref. 7). High percentage oily solutions (e.g., 50 percent) are used to destroy keratin down to the corium for cosmetic repair (Ref. 5). Phenol is less soluble in water than in alcohol and penetrates deeply into the skin producing severe burns, and is absorbed in higher concentrations producing systemic effects (Ref. 4).

Systemically, phenol can cause central nervous system depression. It decreases blood pressure partly as a result of central vasomotor depression, but mainly due to a direct toxic action on the myocardium and the smaller coronary blood vessels. Because it is lipid soluble, phenol can be absorbed into the circulation even from intact skin (Ref. 1).

(3) *Effectiveness.* Phenol acts both systemically and locally. Phenol disassociates from combination with protein and has great penetrability into tissues. When applied directly to skin, a white pellicle (layer) of preicipitated protein is formed. If phenol remains in contact with skin for a prolonged period of time, phenol penetrates deeply and may cause extensive necrosis (Refs. 1, 3, and 4).

(4) *Evaluation.* Phenol is rarely used as an antiseptic. It was widely used and accepted as an antiseptic when little else was available. Now it is obvious that the level of phenol required in an antiseptic formulation to be effective (i.e., 2 percent or greater) is higher than the level that can be safely used on skin or mucous membranes. Phenol is toxic in concentrations greater than 1.5 percent (Ref. 5).

Refereneces

(1) Esplin, D. W., "Antiseptics and Disinfectants; Fungicides: Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, pp. 1032–1066, 1970.

(2) "AMA Drug Evaluations—1973," 2d Ed., American Medical Association, Action, MA, pp. 653–654 and 665, 1973.

(3) Deichmann, W. B. and M. L. Keplinger, "Phenols and Phenolic Compounds," *in* "Industrial Hygiene and Toxicology," Volume II, 2d Rev. Ed., Edited by Patty, F. A., Interscience Publishers, New York, 1963.

(4) Deichmann, W. B., "Local and Systemic Effects Following Skin Contact with Phenol. A Review of the Literature," *Journal of Industrial Hygiene and Toxicology*, 31:146–154, 1949.

(5) Brown, A. M., L. M. Kaplan and M. E. Brown, "Phenol-induced Histological Skin Changes: Hazards, Techniques, and Uses," *British Journal of Plastic Surgery*, 3:158–169, 1960.

(6) Wright, A. D., "Complications of Rectal Injection," *Proceedings of the Royal Society of Medicine*, 43:263–266, 1950.

(7) Jacoby, J. J. and H. M. Livingstone, "Topical Anesthesia of the Intact Skin," *The Military Surgeon*, 107:282–284, 1950.

e. *Resorcinol (intrarectal use).* The Panel concludes that resorcinol is not safe or effective for intrarectal use as an antiseptic in OTC anorectal preparations.

(1) *Description.* (See part X. paragraph B.1.b. (1) below—Description.)

(2) *Safety.* (See part X. paragraph B.1.b. (2) below—Safety.) Absorption of resorcinol may occur through the skin, through open wounds, or from the gastrointestinal tract (Refs. 1, 2, and 3). Resorcinol resembles phenol in its physiologic properties so that the effects are very similar (Ref. 1). Phenol absorption from the bowel takes place rapidly and in a few instances has led to severe and fatal poisoning after such superficial exposure that hypersensitivity or idiosyncracy is suggested (Ref. 2).

Resorcinol has been employed in the past in various preparations taken by mouth but is no longer available because of potential for toxicity. At present it is used in some intrarectal applications. However, rapid absorption occurs from mucous membranes (Refs. 2 and 4). A 3 percent concentration in 1 ounce (oz) (28.5 g) of ointment would provide 840 mg of resorcinol; this is a toxic dose if it were inserted in the rectum and absorbed rapidly (Ref. 2). The Panel agrees with a standard pharmaceutical reference that states that resorcinol has no legitimate internal use (Ref. 5).

(3) *Effectiveness.* Resorcinol resembles phenol in its physiologic properties, though it is less active (Refs. 3, 4, and 6). Klarmann, Gatyas, and Shternov (Ref. 7) found that the phenol coefficient against *Typhoid bacillus* or *Staphylococcus aureus* was 0.4. Therefore, the effective concentration of resorcinol would be two and one-half times that of phenol. Insofar as aqueous

solutions of phenol are concerned, they are bacteriostatic in vitro in a 0.2 to 1.0 percent concentration, and bactericidal but unsafe at higher concentrations (Ref. 1). Though its actions will vary depending on organisms present and temperature, it would seem reasonable to concude that 0.5 to 2.5 percent resorcinol on intact skin would be bacteriostatic, although its potency as a bactericide would be marginal. However, there is no evidence to document intrarectal effectiveness on mucous membranes.

(4) *Evaluation.* Because of the constant contamination in the rectum, the Panel concludes that intrarectal use is of no value and use of resorcinol in that location as an antiseptic is not warranted.

References

(1) "Martindale. The Extra Pharmacopoeia," 26th Ed., Edited by Blacow, N. W., The Pharmaceutical Press, London, England, p. 201, 1972.

(2) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., The Williams and Wilkins Co., Baltimore, MD, pp. 124 and 189–192, 1969.

(3) DiPalma, J. R., "Drill's Pharamcology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, p. 1640, 1971.

(4) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 1017–1018, 1973.

(5) "Remington's Pharmaceutical Sciences," 14th Ed., Edited by Osol, A. et al., Mack Publishing Co., Easton, PA, pp. 1187–1188, 1970.

(6) Reddish, G. F., "Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization," 2d Ed., Lea and Febiger, Philadelphia, PA, pp. 537–543, 1957.

(7) Klarmann, E., L. W. Gatyas and V. A. Shternov, "Bactericidal Properties of Monoethers of Dihydric Phenols. I. The Monoethers of Resorcinol," *Journal of the American Chemical Society*, 53:3397–3407, 1931.

f. *Sodium salicylic acid phenolate (external and intrarectal use).* The Panel concludes that sodium salicylic acid phenolate is not safe as an antispetic and that there is insufficient evidence to prove effectiveness for use in OTC anorectal preparations.

(1) *Description.* Sodium salicylic acid phenolate is not a known or recognized chemical entity found in the published literature. In the submission to the Panel, from the listed ingredients used to prepare sodium salicylic acid phenolate, it is difficult to determine what chemical reactions actually may occur (Ref. 1). The Panel will evaluate sodium salicylic acid phenolate based on its phenol and salicylic acid components.

(2) *Safety.* No published references were found regarding the safety of this compound; however, it is expected that the effects would be similar to the combination of phenol and salicylic acid. According to information submitted by a manufacturer who utilizes this compound, an analysis reveals that the compound contains nearly all of its phenol as free phenol (Ref. 2). The amount of phenol is reported to be 3.35 percent (Ref. 2). As discussed elsewhere in this document, phenol is not considered safe in concentrations greater than 1.5 percent (Ref. 3). (See part IX. paragraph B.2.d.(2) above—Safety.) Phenol is rarely used as an atiseptic because it has relatively feeble activity, and it possesses undesirable tissue toxicity when used in an effective antiseptic concentration (Refs. 4, 5, and 6).

Salicylic acid is irritating to skin and mucosa, destroying epithelial cells (Ref. 3). It is a keratolytic agent, causing tissue cells to swell, soften, and desquamate (Ref. 3).

(3) *Effectiveness.* No published studies affirming the effectiveness of sodium salicylic acid phenolate have been found.

Salicylic acid is not a recognized antiseptic agent.

Phenol is no longer commonly used as an antiseptic. It is obvious that the level of phenol required in a formulation to be effective as an antiseptic (i.e., 2 percent or greater) is sufficiently high so that it cannot be used safely on the skin or mucous membranes; concentrations greater than 1.5 percent are not generally recognized as safe.

(4) *Evaluation.* The Panel concludes that sodium salicylic acid phenolate is not safe or effective for use as an antiseptic or anorectal ingredient.

References

(1) OTC Volume 120017.

(2) OTC Volume 120043.

(3) Goodman, L. S. and A. Gilman, "The Parmocological Basis of Therapeutics," 5th Ed., The Macmillan Co., New York, pp. 335 and 991, 1966.

(4) Deichmann, W. B., "Local and Systemic Effects Following Skin Contact with Phenol. A Review of the Literature," *Journal of Industrial Hygiene and Toxicology*, 31:146–154, 1949.

(5) "Remington's Practice of Pharmacy," 13th Ed., Edited by Martin, E. W. and E. F. Cook, Mack Publishing Co., Easton, PA, pp. 1440–1441, 1965.

(6) Wright, A. D., "Complications of Rectal Infection," *Proceedings of the Royal Society of Medicine*, 43:263–266, 1950.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of anorectal drug products are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel concludes the following claims to be misleading and unsupported by scientic data.

a. The term"antiseptic" and/or "antisepsis" is not acceptable. The Panel concludes that this term has many varied meanings ranging from partial (static) to total (cidal) effects and has no usefulness in anorectal OTC products because of the large number of organisms that normally exist in the anorectal area.

b. The term "kills" implies a total antisepsis that is useless in the anorectal area even if achieved because of the large number of organisms that normally exist in this area.

c. "Reduces inflammation, kills bacteria, deadens pain and rapidly removes annoying irritation." This claim cannot be justified when associated only with the term antiseptic.

d. "Not only an antiseptic action . . ." This claim is misleading because it implies too wide an effect that cannot be proved and is not useful in anorectal products.

e. "Controls infection" is unacceptable for conditions amenable to OTC treatment; infections require supervision by a physician.

f. The following are claims that are unproven and, due to contamination of the anorectal area following bowel movements, are only an unsubstantiated relative antibacterial activity at best:

(i) "Forms a protective antibacterial film over raw inflamed tissue."

(ii) "Possesses a highly bactericidal and fungicidal effect on the germs, fungi, yeasts, molds, and pathogens present in the infected area."

(iii) "Prevents overt skin infection."

(iv) "Degerming in the anorectal area."

(v) "Bacteriostatic in the anorectal area."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredient

The Panel concludes that the available data are insufficient to permit final classification of the following antiseptic active ingredient named below. The Panel believes it is reasonable to provide 2 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 2 years,

however, the ingredient listed in this category should no longer be marketed in OTC products.

Resorcinol (external use). The Panel concludes that resorcinol is safe for external use as an antiseptic but that there is insufficient evidence to prove effectiveness for use in OTC anorectal preparations.

(1) *Description.* (See part X. paragraph B.1.b. (1) below—Description.)

(2) *Safety.* (See part X. paragraph B.1.b. (2) below—Safety.)

(3) *Effectiveness.* Resorcinol resembles phenol in its physiologic properties, although it is less active (Refs. 1, 2, and 3). Klarmann, Gatyas, and Shternov (Ref. 4), found that the phenol coefficient against *Typhoid bacillus* or *Staphylococcus aureus* was 0.4. Therefore, the effective concentation of resorcinol would be two and one-half times that of phenol. Insofar as aqueous solutions of phenol are concerned, they are bacteriostatic in vitro in a 0.2 to 1.0 percent concentation, and bactericidal at higher concentrations (Ref. 5).The Panel has received letters from recognized dermatologic experts who state that resorcinol is a mild antiseptic in concentrations of 1 to 5 percent (Refs. 6, 7, and 8). Though its actions will vary, depending on organisms present and temperature, it would seem reasonable to conclude that resorcinol in a 0.5 to 2.5 percent concentration would be bacteriostatic, but its potency as a bactericide would be marginal (Refs. 2 and 4). However, in the anorectal area frequent contamination makes resorcinol less effective as an antiseptic. No data were found to indicate the effectiveness of resorcinol less effective as an antiseptic. No data were found to indicate the effectiveness of resorcinol in this area as an antiseptic. If further bacteriologic studies indicate a reduction in the number of bacteria in the perianal area after application of resorcinol, claims for temporary reduction in the number of bacteria, bacteriostatic, degerming, or reduction in the risk of infection could be made. (see part IX. paragraph C. below—Data Required for Evaluation.)

(4) *Proposed Dosage.* Adult external dosage is 0.5 to 2.5 percent per dosage unit not to exceed 50 mg per dosage unit and not to exceed six applications per 24 hours.

(5) *Proposed labeling.* The Panel recommends the Category III labeling for antiseptic active ingredients, pending testing for effectiveness. (See part IX. paragraph B.3. below—Category III Labeling.)

(6) *Evaluation.* The value of any antiseptic in the perianal area is open to question. Heavy contamination and recontamination are the rule so that any claim as an antiseptic needs careful substantiation. The Panel was unable to find any pertinent evidence concerning the bactericidal effect of resorcinol in perianal disease. Because there is a possibility that such evidence could be found, resorcinol is being placed in Category III for external use. Tests to elevate resorcinol to Category I for external use as an antiseptic must include bacteriologic studies to prove bacteriostatic or bactericidal effects for a suitable period of time for gram-negative bacteria, and prove that replacement of these bacteria by other pathogenic organisms or fungi does not occur. These tests are described in detail later in this document. (See part IX. paragraph C. below—Data Required for Evaluation.)

References

(1) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 1017–1018, 1973.

(2) Reddish, G. F., "Antiseptics, Disinfectants, Fungicides and Chemical and Physical Sterilization," 2d Ed., Lea and Febiger, Philadelphia, PA, pp. 537–543, 1957.

(3) DiPalma, J. R., "Drill's Pharmacology in Medicine," 4th Ed., McGraw-Hill Book Co., New York, p. 1640, 1971.

(4) Klarmann, E., L. W. Gatyas and V. A. Shternov," Bactericidal Properties of Monoethers of Dihydric Phenols. I. The Monoethers of Resorcinol," *Journal of the American Chemical Society,* 53:3397–3407, 1931.

(5) Harvey, S. C., "Antiseptics and Disinfectants, Fungicides, Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, pp. 990–993, 1975.

(6) Letter to DeCillis, T. D. from A. A. Fisher dated March 9, 1977 is included in OTC Volume 120051.

(7) Letter to Decillis, T. D. from E. F. Traub dated March 9, 1977 is included in OTC Volume 120051.

(8) Letter to DeCillis, T. D. from R. B. Rees dated March 14, 1977 is included in OTC Volume 120051.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the claims listed below. Additional data are required to support the following antiseptic claims:

a. "Temporarily reduces the number of organisms in the perianal area."

b. "Reduces the risk of infection."

C. Data Required for Evaluation

The Panel has agreed that the protocols recommended in this document for the studies required to substantiate Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodoldgy in the future.

Relative antisepsis. Demonstration of this effect must be carried out in human subjects because of the unique environment of the anorectal area. Proof of relief after repeated applications will be required in addition to noting changes in bacterial counts after one application; the primary purpose is for testing of claims for antisepsis. Therefore, bacteriological colony counts per cm on a sterile 1 cm square pledgett applied to the skin at the anal verge immediately, 30 minutes, 2 hours, and 6 hours after use of the ingredient on the area compared with use of water only or no treatment and exclusion of recent defecation will provide a reasonable measure of this property. If significant differences in bacterial count were found in a statistically significant number of trials, this claim is permitted. However, the claim would have to reflect the actual duration of not less than 30 mimutes of the antiseptic effect found in the studies to the extent that it was statistically superior to soap and water. Consideration of aerobic and anaerobic organisms must also be evaluated.

b. An alternate technique was suggested by Engley (Ref. 1) utilizing a neutralizing medium. A special medium is important to determine the effectiveness of the active ingredient as opposed to the effect of preservatives in the final product.

Five organisms, *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia col, Proteus vulgaris,* and *Pseudomonas aeruginosa,* which are most frequently associated with skin or the perianal area, are streaked with a swab on a blood-agar plate. A 12.5 mm disc, previously coated with a layer of a final formulation product, is placed face down in the center of the streak. The plate is then incubated for 18 hours at 98.6° F (37° C). The zone of inhibition around the disc will give an approximate degree of antimicrobial activity.

Formulations showing inhibition would then be tested for effectivenes in the perianal in the following manner: A cotton swab is used to obtain a sample of the microbial flora of the skin in the test area. The product is applied to the skin for a predetermined length of time (e.g., 20 minutes) and then removed. A second sample is taken immediately after 1, 2, and 4 hours have elapsed. The swab is used to streak a 12 mm zone on a blood-agar plate and then placed on the agar after cutting the stick off the swab. Incubation is done at 98.6° F (37° C) for 18 hours.

Positive results will have to be verified against a special neutralizing media to eliminate the effect of preservatives from the effect of active ingredients. The duration of antisepsis, if achieved, can be evaluated by this technique.

It has not yet been established how long antimicrobial activity must be exhibited and the minimum zone of inhibition required to permit antisepsis claims in the anorectal area. In view of the lack of established procedures for investigating this area, the Panel recommends that FDA work with interested parties to develop the details necessary to illustrate the principles in both techniques discussed here, i.e., (1) the presence of organisms and types after using an anorectal antiseptic and (2) the zone of inhibition on standard organisms.

Reference

(1) Engley, F. B., Presentation to the Panel, July 9, 1976, is included in OTC Volume 120051.

X. Keratolytics

A. General Discussion

The Panel has defined keratolytics as agents that cause desquamation (loosening) and debridement or sloughing of the surface cells of the epidermis. The epidermis consists of stratified squamous cells that contain keratin (Ref. 1). Certain substances, especially the phenols and sulfhydryl compounds, loosen keratin, resulting in debridement and desquamation of epithelial tissue (Ref. 1). Adriani (Ref. 2) was able to demonstrate that resorcinol, which belongs to the class of dihydric phenols, in concentrations of 1 to 3 percent may have some ability to reduce itching as does phenol, although resorcinol is slightly less toxic. Keratolytics are claimed to be useful in many conditions where the keratin layer has proliferated to a great extent, such as warts, corns, psoriasis, eczema, and acne (Refs. 1, 3, and 4) and are being reviewed by other OTC review panels. Because they help remove keratin-containing cells, it is theorized that keratolytics help expose underlying tissue to therapeutic agents; the combination of two or more active ingredients is discussed elsewhere in this document. (See part II. paragraph K. above—Principles Applicable to Combination Products.)

In a presentation to the Panel, Maibach stated that many chemicals are not considered to be keratolytics in the concentrations usually employed and at present there are apparently no good quantitative methods to study the mechanism of action of keratolytics in treating itching (Ref. 5). Maibach could not explain the therapeutic value of using keratolytics on perianal skin, which is usually moist and sometimes macerated, but Maibach thought that keratolytics were of some value in ichthyosis in which the skin is characterized by dryness, roughness, and scaliness due to excessive thickness (hypertrophy) of the horny layer (Ref. 5). The Panel concludes that keratolytics at the concentrations specified in the following ingredient discussions, for external use, are useful in reducing itching, but a claim for keratolysis requires additional study.

Keratolytics have been used intrarectally in OTC anorectal products. The Panel believes it is highly irrational therapy, however, because there is no keratin layer on mucous membranes. Keratolytics are used externally in certain cases of anal hyperkeratinization for example in psoriasis, acne, seborrheic dermatitis, and eczema. However, many anorectal diseases are associated with excoriation or mild inflammation in which dekeratinization has occurred. The Panel also recognizes that there may be conditions in which too high a concentration of keratolytics might produce irritation that would be detrimental to healing. For this reason, safe and effective concentrations of keratolytics to relieve itching or to achieve keratolysis must be carefully established.

References

(1) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by Osol, A. and J. E. Hoover, Mack Publishing Co., Easton, PA, p. 724, 1975.

(2) Adriani, J., "The Chemistry and Physics of Anesthesia," 2d Ed., C. C. Thomas, Springfield, IL, p. 402, 1962.

(3) Swinyard, E. A., "Surface-Acting Drugs," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, p. 953, 1975.

(4) Swinyard, E. A. and S. C. Harvey, "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 13th Ed., Edited by Martin, E. W., Mack Publishing Co., Easton, PA, p. 861, 1965.

(5) Minutes of the OTC Panel on Hemorrhoidal Drug Products, 23d meeting, November 21, 22, and 23, 1976.

B. Categorization of Data

1. *Category I conditions under which keratolytic ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients

The Panel has classified the following keratolytic active ingredients as generally recognized as safe and effective and not misbranded:

Alcloxa (external use)

Resorcinol (external use)

a. *Alcloxa (external use).* The Panel concludes that 0.2 to 2.0 percent alcloxa per dosage unit is safe and effective for external use as a keratolytic for the relief of itching in OTC anorectal preparations and not to exceed six applications per 24 hours.

(1) *Description.* Alcloxa (aluminum chlorhydroxy allantoinate) is a clean, white powder that is soluble in water and to a lesser extent in alcohol. It is insoluble in ether and chloroform (Ref. 1). Allantoin (5-ureidohydantoin) is a uric acid derivative and is chemically known as the diureide of glyoxyllic acid. In the racemic form, allantoin appears as monoclonic prisms or plates; it is in the form of colorless crystals (Refs. 2, 3, and 4).

In 1568, the virtues of comfrey root, the natural predecessor of allantoin, as a keratolytic and protectant were described (Ref. 1). During the Civil War it was observed that wounds that were infested with living maggots (maggots excrete allantoin) healed rapidly (Ref. 1).

(2) *Safety.* No reports have been found indicating any significant toxicity of allantoins as keratolytics in topical preparations in a concentration range of 0.2 to 2.0 percent. Patch testing and repeated insult testing on humans showed that allantoin is nontoxic, nonirritating, and nonallergenic and that it was not a primary skin sensitizer (Ref. 4). Testing on rabbits showed that allantoin is nonirritating to the eye (Ref. 4).

Allantoin has been demonstrated as having a keratin and protein dispersal effect (Ref. 4). The dispersal effect is in part due to action on the soluble cement substance (keratin matrix) which is responsible for the adherence of the cornified cells in the stratum corneum to each other (Ref. 5). There have been no reports of the growth of abnormal tissue or tumors with the use of allantoin (Ref. 4).

In animal experiments (Ref. 4), aluminum chlorhydroxy allantoinate was applied to a 4 square inch (in^2) shaved area on the backs of adult male guinea pigs, and the chemical agent proved to be without any primary irritating or sensitizing properties.

(3) *Effectiveness.* The Panel concludes that allantoin can reduce itching, although the mechanism is unclear. A therapeutic quality of the allantoins is

said to be a healing effect, which is attributed to cell proliferant action and its effectiveness in removing necrotic tissue (Ref. 2). It is reported to be safe, soothing, and nonirritating even after relatively constant use for extended periods of time (Ref. 4). Aluminum chlorhydroxy allantoinate and other aluminum derivatives of allantoin, in addition to the therapeutic properties of allantoin, are said to exert astringent, buffering, and deodorant effects (Ref. 1). It is reported safe and effective in the forms of powder, solution, suspension, cream, lotion, or ointment (Ref. 3).

The Keratolytic activity of aluminum chlorhydroxy allantoinate is related to the fact that the allantoin is a hydrogen bond breaker. It probably acts by a desolvating action on the mucopolysaccharide, whose presence has been indicated in the intercellular cement of the stratum corneum (Ref. 4).

Allantoin also has a protein denaturing effect on the soluble proteins in the cement matrix by splitting their disulfide linkages, as evidenced by exposure of sulfhydryl groups whose presence can be determined by appropriate chemical means (Refs. 4 and 6).

When allantoin is applied to ulcers, wounds, cuts, and lacerations, it is claimed to have the ability to remove the undesirable necrotic tissue, clean up the area, and then follow through by inducing new tissue growth.

Another reported activity is that it appears to produce a medium distinctly unfavorable to bacterial growth. Allantoin is also said to possess leukocytic stimulating properties, particularly by stimulating healthy neutrophils (Ref. 4). The mechanism by which allantoin relieves itching is not clear, but the property of aiding in the removal of necrotic tissue and/or the possible stimulation of healing could lead to this effect. Data submitted contain studies on a range of concentration used from 0.2 to 2.0 percent (Refs. 4 and 7).

(4) *Dosage.* Adult external dosage is 0.2 to 2.0 percent per dosage unit and not to exceed six applications per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for keratolytic active ingredients. (See part X. paragraph B.1. below—Category I Labeling.)

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b. *Resorcinol (external use).* The Panel concludes that 1 to 3 percent resorcinol per dosage unit is safe and effective for external use as a keratolytic for the relief of itching in OTC anorectal preparations and not to exceed six applications per 24 hours.

(1) *Description.* Resorcinol is *m*-dihydroxybenzene. It occurs as white or pearly white, needle-shaped crystals or powder. One g dissolves in about 1 mL of water or alcohol. It is freely soluble in glycerin and ether and slightly in chloroform (Regs. 1 through 3).

(2) *Safety.* Therapeutic results and toxicity are closely related to the concentration of the agent employed and the site of application. The amount used must be limited because the toxicity of resorcinol is high. Absorption has led to methemoglobinemia, exfoliative dermatitis and death in infants, and to myxedema after repeated application in adults. Resorcinol can be absorbed rapidly from mucous membranes and is more dangerous than application to the intact skin. Severe allergic reactions may occur (Refs. 1, 4, 5, and 6).

In rats the subcutaneous minimal lethal dose is 450 mg/kg. The probable lethal dose of resorcinol in humans is between 50 to 500 mg/kg in a 7-kg man (Ref. 4). Dreisbach (Ref. 7) accepts a lower minimal figure of 2 g in a 70-kg man. The total maximum daily dose, even assuming complete absorption, to which an adult is exposed when resorcinol is used according to the recommended dosage set by the Panel is 360 mg in a 70-kg man (5.14 mg/kg). Therefore, the Panel concludes that resorcinol is safe at the recommended dosage because the total maximum recommended dose of 360 mg is considerably less than the 2-g toxic dose set by Dreisbach (Ref. 7).

Absorption of resorcinol may occur through the skin, through open wounds, or from the gastrointestinal tract. Resorcinol resembles phenol in its physiologic properties so that the effects are very similar (Ref. 1). Phenol absorption from the bowel takes place so rapidly, and in a few instances has led to severe and fatal poisoning after such superficial exposure, that hypersensitivity or idiosyncracy is suggested (Ref. 4). Similarly, after two applications of resorcinol to nearly intact skin, Kyrle (Ref. 5) noted poisoning in a 2-day-old infant.

The symptoms of mild resorcinol poisoning are ringing in the ears, some acceleration of breathing or pulse, and profuse sweating. With large doses, methemoglobinemia, circulatory collapse, unconsciousness, and violent convulsions may occur. Enough resorcinol may be absorbed from the essentially intact skin or from ulcerations to produce toxic effects (Refs. 1, 4, 5, and 6).

In vitro exposure of red blood cells to resorcinol produced a gradual swelling and an increase of the cell volume by 25 percent. This was followed by hemolysis (Ref. 8).

Fatal resorcinol poisoning has been reported in infants, though the Panel has found no report of deaths in adults. Cunningham (Ref. 9) reported a case of an infant who, after application of a compound containing 12.5 percent resorcinol (a total of 1.0 to 1.25g), developed methemoglobinemia and exfoliative dermatitis. Recovery was still incomplete 6 months later. Cunningham (Ref. 9) collected from the literature eight somewhat similar infant cases. Most of the infants had perianal eczema or diaper rash; seven of them died shortly after application. The concentration of resorcinol, known in three instances, was 2 percent, 3 percent, and 5 percent, but the quantity used resulted in toxicities. Castellani's solution which contains 10 percent resorcinol, led to methemoglobinemia with conversion of 41 percent of the hemoglobin when painted twice on a 6-month-old infant (Ref. 10).

Several adults have developed myxedema due to the antithyroid action of the drug following absorption when applied repeatedly to varicose ulcers (Refs. 11, 12, and 13). In rats subcutaneous injections of resorcinol diacetate markedly reduced radioactive iodine uptake in the thyroid, and injections twice daily at a dose of 0.4 millimoles per 100 grams produced thyroid hyperplasia in 12 days (Refs. 14 and 15).

Resorcinol, like phenol (Ref. 4), can produce a severe allergic reaction either immediately or after subsequent application (Ref. 7). Considering the large number of applications of resorcinol in various preparations, the overall sensitizing potential, however, is low (Refs. 1 through 4).

An unpublished study on 51 patients suggests that clincially significant irritation occurs at concentrations greater than 5 percent resorcinol when applied as an occlusive patch for 48 hours (Ref. 16). This is further evidence that resorcinol is safe in concentrations of 1 to 3 percent recommended by the Panel.

In summary, the Panel concludes that resorcinol used externally in adults in a 1 to 3 percent concentration in anorectal OTC drug products is safe when accompanied by a warning, "Do not use in open wounds near the anus," and notes that numerous clinical trials (Refs. 17, 18, and 19) of preparations containing such concentrations of resorcinol testify to its safety.

(3) *Effectiveness.* A major action of resorcinol is as a keratolytic agent (Refs. 1, 2, and 3). Resorcinol is considered to have an antipruritic action and although the exact mechanism of its ability to relieve itch is not known, the Panel finds that resorcinol is effective for this purpose (Refs. 17 through 22). With pastes that contain as much as 45 percent resorcinol, the entire thickness of skin may be destroyed (Ref. 23). Application of resorcinol, though effective, must be limited to very short periods (e.g., 24 hours or less) because of absorption and toxicity (Refs. 1, 2, and 3).

There is no complete agreement concerning the lowest concentration in which resorcinol is effective as a keratolytic. Several authorities consider the lowest level to be 1 percent. Grollman and Grollman (Ref. 24) accept a 1 to 5 percent concentration for a keratolytic effect; others accept a 2 percent level (Refs. 1 through 3). The Panel received letters from recognized dermatology experts who state that resorcinol is a mild keratolytic in concentrations of 1 to 3 percent (Refs. 17, 18, 20, 21, 22, and 25). Ormsby and Montgomery (Ref. 19) state that it is keratoplastic in solutions of 2 to 4 percent concentration and is keratolytic in a strength of 10 to 50 percent.

Keratolytics in the anorectal area are of value in the treatment of psoriasis or for the removal of the outer layer of the thickened epidermis (Refs. 1 and 26). The Panel is aware that OTC products for the treatment of psoriasis are being reviewed by another OTC advisory review panel and that claims for psoriasis will be more appropriately reviewed by that Panel.

Many cases of anorectal disease are characterized by skin abrasions or infection in which excessive keratolysis theoretically could exert adverse effects that should be under physician supervision. For this reason, the Panel has accepted low concentrations of resorcinol (1 to 3 percent) as of value in anorectal products for external use.

(4) *Dosage.* Adult external dosage is 1 to 3 percent per dosage unit and not to exceed six applications per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for keratolytic active ingredients. (See part X. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following warnings: (i) *"Caution:* Certain persons can develop allergic reactions to ingredients in this product. If redness, irritation, swelling, pain or other symptoms develop or increase, discontinue use and consult a physician."

(ii) "Do not use in open wounds near the anus." The warning is considered necessary to preclude absorption of resorcinol through broken skin.

(6) *Minority report on resorcinol.* The minority concludes that resorcinol has no proven effectiveness as a kerotolytic at 1 to 3 percent concentrations, which are possibly safe for topical use, although the safety for OTC use is also unproven.

(i) *Safety.* Resorcinol, like phenol, is a toxic substance whose adverse effects can result from both exposure to an excessive dose on one occasion or chronic exposure to lower doses (Refs. 1, 4, 5, 6, 11, 12, and 13). Although these hazards can be weighed against therapeutic benefits when physician-supervised dermatologic therapy is undertaken, the minority of the Panel concludes that the safety of 1 to 3 percent resorcinol for external use in the OTC market remains to be established.

(ii) *Effectiveness.* Resorcinol is an effective keratolytic by virtue of its ability to alter keratin and increase the pliability, or plasticity, of the keratin layer of skin (Ref. 5). This effect also secondarily interrupts the keratin epithelial barrier of the skin to allow increased absorption of itself and any other substances present. The ability to soften keratin is a useful property in the treatment of disorders characterized by hyperkeratinization, such as psoriasis or simple callouses.

The anorectal area is characteristically moist due to anatomical factors and occlusion by clothing. This fact helps contribute to the pliability of the skin surface in this area. The anorectal area is only rarely plagued by disorders of hyperkeratinization such as psoriasis or venereal disease, which are usually treated by a physician. The former is more likely treated with steroids rather than keratolytics. If the latter (venereal disease) is treated with a keratolytic, it is applied in concentration only to the lesion for a specific time period and removed to avoid toxicity. The more common lesions of the anorectum such as anal fissures, enlarged hemorrhoidal veins, and perianal skin irritation of a moist type are not pathologically characterized by hyperkeratinization. Therefore, the minority are unable to conclude a keratolytic has any rationale for OTC anorectal use.

A further problem arises when the amount used for purported keratolytic effects is considered. There is controversy in the secondary resource literature regarding the lowest effective keratolytic concentration, which ranges from an estimate of 1 to 10 percent (Refs. 1, 2, 3, 5, and 25). Much of the confusion arises due to the lack of any careful studies to establish this fact. The majority opinion of the Panel is that resorcinol is safe at concentrations less than 3 percent and effective as a keratolytic in concentrations of 1 to 3 percent. There are no studies found which establish this property at this concentration on any body site or in the anorectal area.

Therefore, it is the opinion of three Panel members that proof of effectiveness of resorcinol as a keratolytic for use in the anorectal area needs to be established with regard to both therapeutic usefulness and rationale for the OTC market and, if established, the effectiveness of the proposed safe dose in the anorectal area.

(iii) *Studies needed for proof of safety and effectiveness*—(*a*) *Safety.* The primary safety concerns relate to absorption of resorcinol systemically. If any absorption from abraded skin areas can demonstrate quantities of resorcinol in blood level or urinary excretion, then that quantity of resorcinal should be studied to determine whether toxic effects will occur. Methods to determine the effects could include red cell function, and liver and renal function tests. Since resorcinal has been reported to induce goiten and tinnitus, thyroid function test and auditory function test could also be used. If absorption is not demonstrated, it must be established, by use of animal models if needed, that the lower limit of sensitivity of assay method would measure blood or urine levels expected with administration of known toxic levels. For example, in rats, the minimal lethal dose is 450 mg/kg. By administration of lower amounts and measurements of kinetics, estimates of volume of distribution and correlation of blood level with total dose can be made, and a toxic blood concentration can be estimated and correlated with dose. If the method is adequately sensitive and

no absorption is demonstrated, this would be acceptable evidence of relative safety.

(*b*) *Effectiveness.* (*1*) Statistically significant clinical improvement in symptoms of anorectal disease with resorcinol in final formulation compared to final formulation alone, in double-blind clinical trials as well as demonstration that this improvement is due to keratolysis, would be necessary to substantiate a claim for improvement in symtoms due to keratolysis, although only the former is needed to claim symptomatic improvement.

(*2*) The effectiveness of 1 to 3 percent resorcinol in formulation giving symptomatic improvement and achieving keratolysis must be demonstrated if a claim is made for effectiveness by virtue of keratolysis.

(*3*) The property of keratolysis may be demonstrated histologically and possibly by a test of tensile strength or compressibility and could be done on skin from other body sites.

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(1) "The United States Dispensatory," 27th Ed., Edited by Osol, A. and R. Pratt, J. B. Lippincott Co., Philadelphia, PA, pp. 1017–1018, 1973.

(2) "The United States Pharmacopeia," 19th Rev., The United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 440–441, 1975.

(3) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1058, 1976.

(4) Gosselin, R. E. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," 4th Ed., The Williams and Wilkins Co., Baltimore, MD, p. 128, 1976.

(5) Kyrle, J., "Beitrag zur Kenntnis der Resorzinvergiftung bei ausserer Applikation des Mittels," *Dermatologische Zeitschrift,* 22:505–510, 1915.

(6) Wuthrich, B., S. Zabrodsky and H. Storck, "Perkutane Vergiftungen durch Resorcin, Salicylsaure und weisse Pracipitatsalbe," *Pharmaceutica Acta Helvetiae,* 45:453–460, 1970.

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(8) Latta, H., "Anomalous Swelling of Erythrocytes Exposed to Resorcinol," (Abstract), *Biological Abstracts,* 46:480, 1965.

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(10) Lundell, E. and R. Nordman, "A Case of Infantile Poisoning by Topical Application of Castellani's Solution," *Annals of Clinical Research,* 5:404–406, 1973.

(11) Hobson, Q. J. G., "Varicose Ulceration of the Legs and Myxoedema and Goitre Following Application of Resorcinol Ointment," *Proceedings of the Royal Society of Medicine,* 44:164–166, 1951.

(12) Berthezene, F. et al., "Resorcin Induced Hypothyroidism," *Lyon Medical,* 230:319–323, 1973.

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(16) OTC Volume 120004.

(17) Letter to DeCillis, T. D. from E. F. Traub, dated February 27, 1976 is included in OTC Volume 120051.

(18) Letter to DeCillis, T. D. from A. A. Fisher, dated February 20, 1976 is included in OTC Volume 120051.

(19) Ormsby, O. S. and H. Montgomery, "Diseases of the Skin," 8th Ed., Lea and Febiger, Philadelphia, PA, p. 145, 1954.

(20) Letter to DeCillis, T. D. from R. B. Rees, dated March 14, 1977 is included in OTC Volume 120051.

(21) Letter to DeCillis, T. D. from E. F. Traub, dated March 9, 1977 is included in OTC Volume 120051.

(22) Letter to DeCillis, T. D. from A. A. Fisher, dated March 9, 1977 is contained in OTC Volume 120051.

(23) "American Hospital Formulary Service," American Society of Hospital Pharmacists, Washington, DC, 84:28, 1976.

(24) Grollman, A. and E. F. Grollman, "Pharmacology and Therapeutics," 7th Ed., Lea and Febiger, Philadelphia, PA, pp. 669 and 961, 1970.

(25) Letter to DeCillis, T. D. from R. B. Rees, dated February 20, 1976 is included in OTC Volume 120051.

(26) Swinyard, E. A. and S. C. Harvey, "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 14th Ed., Edited by Osol, A. et al., Mack Publishing Co., Easton, PA, pp. 1187–1188, 1970.

Category I Labeling

The Panel recommends the following Category I Labeling for keratolytic active ingredients to be generally recognized as safe and effective and not misbranded.

Indication. "For the temporary relief of itching."

2. *Category II conditions under which keratolytic ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

The Panel has classified the following keratolytic active ingredients as not generally recognized as safe and effective or as misbranded:

Precipitated sulfur (intrarectal use)
Sublimed sulfur (intrarectal use)
Resorcinol (intrarectal use)

a. *Precipitated sulfur and sublimed sulfur (intrarectal use).* The Panel concludes that Precipitated sulfur and sublimed sulfur are not effective for intrarectal use as keratolytics in OTC anorectal preparations.

(1) *Description.* The element sulfur exists in a variety of physical forms and is used in fine powders (sublimed or precipitated sulfur), in colloidal form with aqueous solutions, and in ointments (Ref. 1). It is insoluble in water an most organic solvents and may contain small amounts of hydrocarbons and occasionally selenium or arsenic (Ref. 2). It has been used an an antimicrobial agent and more recently as a keratolytic agent for cutaneous disorders (Ref. 1).

(2) *Safety.* No information applicable to safety in anorectal use has been found, although effets when used elsewhere are or relevance to both intrarectal and external use. When given orally, sulfur is reported to have a cathartic effect, probable secondary to formaton of sulfides or sulfates by intestinal bacteria (Refs. 3 and 4), but no maximal toxic dose has been established. It is possible that intrarectal sulfur breaks down in the presence of bacterial flora, which could cause the rare and relatively benign sulfhemoglobinemia (Refs. 1 and 5), although this is unusual in humans (Ref. 6).

When used on human skin, it has been found that elemental sulfur can cause perpetuation and production of acne and follicular obstruction at concentrations greater than 0.5 percent (Ref. 7). Accordingly, concentrations must be kept below this level. A keratolytic agent is judged by the Panel to be deleterious on rectal mucosa.

(3) *Effectiveness.* Clinical studies related to the use of sulphur on rectal mucosa could not be found in the literature. This, plus the lack of any apparent function as judged by the Panel, formed the basis for the Panel's decision that sulfur has no apparent usefulness when used intrarectally.

(4) *Evaluation.* It is irrational to use keratolytics intrarectally. The Panel finds no data to support the safety or effectiveness of the intrarectal use of sulfur.

References

(1) Esplin, D. W., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, pp. 1032–1066, 1970.

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(7) Mills, O. H. and A. M. Kligman, "Is Sulphur Helpful or Harmful in Acne Vulgaris?," *British Journal of Dermatology*, 86:620–627, 1972.

b. *Resorcinol (intrarectal use).* The Panel concludes that resorcinol is not safe or effective for intrarectal use as a keratolytic in OTC anorectal preparations.

(1) *Description.* (See part IX. paragraph B.2.e.(1) above—Description.)

(2) *Safety.* (See part IX. paragraph B.2.e.(2) above—Safety.) Resorcinol has been employed in the past in various preparations taken by mouth. At present it is used in some intrarectal applications. Rapid absorption occurs from mucous membranes (Ref. 1). A 3 percent concentration in 1 oz (28.5 g) of ointment would provide 840 mg of resorcinol, a toxic dose if it were absorbed rapidly from the rectal mucosa. The Panel agrees with a standard pharmaceutical text that states that resorcinol has no legitimate internal use (Ref. 2).

Resorcinol can produce a severe allergic reaction either immediately or after subsequent application. Considering the large number of applications of resorcinol in various preparations, the overall sensitizing potential, however, is low (Refs. 1 through 4).

(3) *Effectiveness.* The intrarectal application of a keratolytic can serve no useful purpose, and almost certainly will aggravate any existing disease because it will act as an irritant. Keratolytics exert a beneficial effect only when applied externally.

The Panel, therefore, concludes that resorcinol has no rational scientific basis for being included in OTC anorectal preparations for intrarectal use.

(4) *Evaluation.* Keratolytics have no reason to be used in intrarectal applications. There are no data to establish safety or effectiveness of resorcinol for intrarectal use and it is, therefore, placed in Category II.

References

(1) "Martindale. The Extra Pharmacopoeia," 26th Ed., Edited by Blacow, N. W., The Pharmaceutical Press, London, England, pp. 571–572, 1972.

(2) Swinyard, E. A. and S. C. Harvey, "Antimicrobial Drugs," *in* "Remington's Pharmaceutical Sciences," 14th Ed., Edited by Osol, A. et al., Mack Publishing Co., Easton, PA, pp. 1187–1188, 1970.

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(4) "The United States Pharmacopoeia," 19th Rev., The United States Pharmacopoeial Convention, Inc., Rockville, MD, pp. 440–441, 1975.

Category II Labeling

None.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the keratolytic active ingredients listed below. The Panel believes it is reasonable to provide 2 years for the development and review of such data. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness and/or safety data are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed in OTC products:

Precipitated sulfur and sublimed sulfur (external use). The Panel concludes that precipitated sulfur and sublimed sulfur are safe for external use as a keratolytic at the proposed dosage, but there are insufficient data to prove effectiveness for use in OTC anorectal preparations.

(1) *Description.* (See part X. paragraph B.2.a(1) above—Description.)

(2) *Safety.* (See part X. paragraph B.2.a.(2) above—Safety.)

(3) *Effectiveness.* Sulfur has been used as a keratolytic agent in the treatment of acne but has not been shown to be effective in the treatment of anorectal disease (Ref. 1). Although no studies pertaining to the usefulness of sulfur in anorectal products were found, the Panel concludes that keratolytics demonstrated at other skin sites may apply here, although demonstration of this effect in safe doses is needed. Concentrations of sulfur at less than 0.1 percent in any vehicle are unlikely to be effective (Ref. 1).

(4) *Proposed dosage.* Adult external dosage is 2 to 10 mg per dosage unit and not to exceed six applications per 24 hours.

(5) *Labeling.* The Panel recommends the Category I labeling for keratolytic active ingredients. (See part X. paragraph B.1. above Category I Labeling.)

Reference

(1) Esplin, E. W., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 1032–1066, 1970.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the following claims. Additional data are required to support the following keratolytic claims:

a. "* * * but is keratolytic, softening the outer skin layers for more effective results."

b. "* * * for more effective results."

C. Data Required for Evaluation

The Panel has agreed that the protocols recommended in this document for the studies required to substantiate Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

Principles in the design of an experimental protocol for testing keratolytic drug—a. *General principles.* Proof of keratolytic activity by an ingredient in the anorectal area would be difficult to demonstrate except by use of biopsy of the affected skin before and after use of the ingredient. Therefore, such testing may be performed on other body sites.

b. *Selection of patients.* Normal human volunteers or persons with hyperkeratotic conditions may be used to establish effectiveness of active ingredients.

c. *Methods of study.* The minimum number of visits should be the initial visit and a follow-up not more than 7 days. Double-blind studies on randomly selected patients should include the use of a fixed focus camera and a grading system.

d. *Interpretation of data.* Desquamation of tissue and necrosis of epithelial cells must be demonstrated within 7 days. Histological examination must give clear evidence of keratolysis.

XI. Anticholinergics

A. General Discussion

An anticholinergic is defined as a substance that inhibits or prevents the action of acetylcholine, the transmitter of cholinergic nerve impulses.

Anticholinergics produce their action systemically at ganglionic synapses, the endings of postganglionic parasympathetic nerves, the neuromuscular junction, and the central nervous system. There is no hypothetical or demonstrated evidence that anticholinergic agents have any role in the relief of anorectal symptoms. Drugs are preferred that limit their therapeutic effect to the particular site involved in the disorder under treatment; other actions constitute side effects. Anticholinergics have no proven controlled local or limited site of action without associated systemic effects.

The Panel finds that no claims were submitted for consideration that were attributed specifically to atropine (belladonna alkaloids). Further, the Panel concludes that anticholinergics as ingredients in OTC anorectal products are not generally recognized as safe and effective because of possible systemic toxicity resulting from unpredictable absorption, e.g., urinary retention, blurred vision, and dry mouth. No reports have been found to indicate that anticholinergics have any specific therapeutic local effects useful in treating anorectal symptoms.

The Panel concludes that any labeling, which is attributed to atropine (belladonna alkaloids and belladonna extract), is misleading and contains unacceptable claims for preparations used for the treatment of anorectal disorders.

B. Categorization of Data

1. *Category I conditions under which anticholinergic ingredients are generally recognized as safe and effective and are not misbranded.*

None.

2. *Category II conditions under which anticholinergic ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredient

The Panel has classified the following anticholinergic active ingredient as not generally recognized as safe and effective or as misbranded:

Atropine and belladonna extract (external and intrarectal use). The Panel concludes that atropine and belladonna extract are not safe or effective for use as anticholinergics in OTC anorectal preparations.

(1) *Description.* Atropine occurs as white crystals, usually needle-like, or as a white crystalline powder. Belladonna extract is obtained by extraction of belladonna leaf and contains in each 100 g not more than 1.5 g and not less than 1.35 g of the alkaloids of belladonna leaf (Ref. 1).

(2) *Safety.* No information regarding the toxicity of atropine (belladonna extract) following application to the anorectal area is available. Therefore, conclusions related to the ingredient must be extrapolated from related human use data. Systemic atropine poisoning may result from absorption of the alkaloid from broken or irritated skin (Refs. 2, 3, and 4). Poisoning due to belladonna plasters has been reported (Ref. 5). While there exists some difference of opinion regarding atropine's margin of safety, it is generally considered a potent and toxic drug (Refs. 6 and 7). The point has also been made that intoxication depends primarily on dose and individual susceptibility (Ref. 8).

Because atropine is a drug that requires individual adjustment of oral dosage levels by a physician, and systemic atropine poisoning may result due to the absorption of atropine when applied to the anorectal area, its use in OTC anorectal preparations is not safe.

(3) *Effectiveness.* The Panel has reviewed the literature extensively and can find no definitive clinical data to establish atropine and belladonna extract (belladonna alkaloids) as effective for use in the treatment of anorectal disorders. Nor were any data submitted to the Panel to support any claim for the use of atropine in anorectal disorders. It has no local effect on intact skin and its systemic effect, as described above for the class of anticholinergic ingredients, occurs only after absorption (Refs. 2, 3, and 4) from irritated or broken skin or mucous membranes when applied internally.

(4) *Evaluation.* The Panel concludes that atropine, because of its potent and toxic nature, the variability in response due to individual susceptibility, and no definitive clinical data supporting its effectiveness when applied externally or intrarectally, is not safe or effective for use in OTC anorectal preparations as an anticholinergic.

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, DC, pp. 56 and 58, 1975.

(2) Avidado, D. M., "Krantz and Carr's Pharmacologic Principles of Medical Practice," 8th Ed., The Williams and Wilkins Co., Baltimore, MD, p. 363, 1972.

(3) "AMA Drug Evaluations—1971," 1st Ed., American Medical Association, Chicago, IL, p. 586, 1971.

(4) Thienes, C. H. and T. J. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, PA, pp. 14–15, 1972.

(5) Sims, S. R., "Poisoning Due to Belladonna Plasters," *British Medical Journal,* 2:1531, 1954.

(6) Goodman, L. S. and A. Gilman, "The Pharmacological Basis of Therapeutics," 4th Ed., The Macmillan Co., New York, p. 530, 1970.

(7) Gleason, M. N. et al., "Clinical Toxicology of Commercial Products. Acute Poisoning," The Williams and Wilkins Co., Baltimore, MD, pp. 34–36, 1969.

(8) Deichmann, W. D. and H. W. Gerarde, "Toxicology of Drugs and Chemicals," Academic Press, New York, p. 116, 1969.

Category II Labeling

None.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.*

None.

XII. Miscellaneous Anorectal Ingredients

A. General Discussion

The actions of several ingredients reviewed by the Panel do not fall within the usual pharmacologic groups of local anesthetics, keratolytics, antiseptics, anticholinergics, vasoconstrictors, protectants, conterirritants, astringents, and wound-healing agents. However, these miscellaneous ingredients are found in OTC anorectal products and are discussed individually below.

B. Categorization of Data

1. *Category I conditions under which miscellaneous anorectal ingredients are generally recognized as safe and effective and are not misbranded.* None.

2. *Category II conditions under which miscellaneous anorectal ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC anorectal drug products effective 6 months after the date of publication of the final monograph in the Federal Register.

Category II Active Ingredients

The Panel has classified the following miscellaneous anorectal active ingredients as not generally recognized as safe and effective or as misbranded:

Collinsonia extract (external and intrarectal use)

E. coli vaccines (external and intrarectal use)

Lappa extract (external and intrarectal use)

Leptandra extract (external and intrarectal use)

Mullein (external and intrarectal use)

a. Collinsonia extract (external and intrarectal use). The Panel concludes that there are no data to establish either the safety or effectiveness of collinsonia extract in OTC anorectal preparations.

(1) *Description.* Collinsonia consists of the dried root of *Collinsonia canadensi.* On analysis, collinsonia contains a resin, saponin, tannin, and mucilage (Refs. 1 and 2). No pharmacologic studies have been reported during the period 1960 to 1975 (Ref. 3).

(2) *Safety.* No data on either the safety or effectiveness of collinsonia have been found in any of the modern texts of pharmacology or in the literature for the past 15 years.

It has been used externally for wounds or as a gargle in the strength of 1 part of fluidextract to 3 parts of water. Used internally, 0.12 to 0.25 g was the accepted dose (Ref. 1). However, because no references were found referring to adverse effects, safety limits are impossible to determine. The presence of tannins introduces a potential danger. There are no reports available on anorectal use.

(3) *Effectiveness.* Collinsonia has been listed as an antispasmodic, diuretic, astringent, anticatarrhal, and diaphoretic used for dropsy, gravel, leukorrhea, cystitis, and inflammatory conditions of the genitourinary organs (Ref. 2). Older herbal medical books describe its use for lochial colic; snake bites; rheumatism; dumb ague; as a vulnerary for dropsy; as a poultice for bruises, sores, blows, falls, wounds, sprains, contusions; taken like tea for headaches, colics, cramps, dropsy, indigestion, bladder pains, ascites, and dropsy of the ovaries; as a powerful tonic in putrid and malignant fevers and in leukorrhea; and for chronic diseases of the respiratory tract, as an agent to relieve pulmonary irritation and a stimulant expectorant for irritation of the pneumogastric nerve (Ref. 4). It has been recommended as a cure for hemorrhoids when taken in oral doses of 1 to 2 drops of the tincture in water three or four times daily (Ref. 4).

The only evidence that would indicate that it is effective for use in anorectal disease consists of a few testimonials submitted in which it was used in combination with other ingredients (Ref. 4).

The disappearance of this ingredient from all modern texts and the fact that no new evidence has been presented concerning its effectiveness in the last 15 years are evidence that this is an outmoded form of treatment.

(4) *Evaluation.* The Panel concludes that there are no data to establish either the limits of safe application or any evidence of the effectiveness of collinsonia for use in anorectal preparations. It is therefore placed in Category II.

References

(1) "The Merck Index," 8th Ed., Merck and Co., Inc., Rahway, NJ, p. 279, 1968.

(2) "The Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 319, 1976.

(3) OTC Volume 120057.

(4) OTC Volume 120053.

b. *E. coli vaccines (external and intrarectal use).* The Panel concludes that *E. coli* vaccines are not safe and effective for use in OTC anorectal preparations.

(1) *Description.* A milliliter of *E. coli* vaccine contains approximately 2,000,000,000 killed *E. coli* (Ref. 1). The method by which the bacteria are killed is not specified. The breakdown products are not specified except as metabolic and corpuscular elements, nor are the strains of *E. coli* employed in the preparation listed.

Preservation is secured by the addition of 2 percent liquefied phenol. However, the data concerning *E. coli* vaccines that have been presented to the Panel specify diluted vaccine so that only 0.4 percent of liquefied phenol is present (Ref. 1).

(2) *Safety.* Animal and human safety data that are available are sparse. Fifty rats were treated with *E. coli* vaccines placed into the wounds, and the tensile strength of these wounds were tested later; complication rates were identical with controls (Ref. 1).

Only two trials in humans have been reported; 40 patients in one trial and 54 patients in the other showed no evidence of local irritation (Ref. 1). Marketing data submitted by the company state that in 50 years the company producing this vaccine has never received nor heard of any reports of side effects (Ref. 1).

The Panel finds that these observations suggest that the product is safe, but are not extensive enough to warrant a firm conclusion.

(3) *Effectiveness.* To obtain a broader base for evaluating this ingredient, the Panel called in a consultant who was also a member of an Advisory Panel to the FDA, Bureau of Biologics (Ref. 2). This discussion incorporates his insight into the data as well as that of the Panel.

It is postulated by the manufacturer that the bacterial culture suspension breakdown products that are incorporated in the preparation act as local vaccines and induce immunologically mediated local resistance (i.e., stimulate the body's natural defenses in the anorectal area) against secondary infections that occur in anorectal disease. The Panel recognizes the need for the consumer to self-treat the limited symptoms of anorectal disorders such as burning, itching, pain, and swelling. If these symptoms persist beyond 7 days, a physician should be seen. It is the experience of the Panel that if secondary infection occurs, there is an important causative factor and may be of a serious nature that requires close supervision by the physician. Normal body defenses operate to prevent secondary infections in the presence of hemorrhoids or swollen tissue so that effectiveness studies would need to show a decrease in the number of infections occuring when compared to normal body defense mechanisms.

In the reports available, the effectiveness of *E. coli* vaccines cannot be separated from other components in the combination that apparently has been used in all experiments.

Evidence of effectiveness presented by the manufacturer includes the following animal experiments. In the first, rabbits were hypo-immunized against *E. coli* by subcutaneous injection of vaccine. After later subjecting the animals to a challenge by painting *E. coli* on the skin, serum titers became higher in the animals who had the injections (Ref. 1). The interpretation was that a measure of immunity could be obtained by painting lyophilized vaccine on intact skin. In another experiment, oral administration of lyophilized vaccine of inactivated *Salmonella typhi murium* protected mice against later oral administration of virulent *S. typhi murium* (Ref. 1). No evidence has been presented that *E. coli* vaccines applied intrarectally will increase the antiboyd titer to *E. coli.*

E. coli includes a large number of organisms that are classified in three large groups. Ewing (Ref. 3) states that 149 O antigens, 91 K antigens, and 51 H antigens are now known. Specific antigens for a number of these groups can be prepared. Oral administration of two strains of live *E. coli* have been reported to increase antibodies to these strains and also to *H. influenza* in adult volunteers (Ref. 4). However, the extent of cross reactivity to other strains of *E. coli* is not clear. furthermore, Sanford has presented data to the Panel (Ref. 2) that American investigators have not been able to effect immunization against *Salmonella* organisms.

No evidence is supplied to indicate that any immunity, if secured for *E. coli*, would be exerted preferentially in the anorectal area. Furthermore, even if *E. coli* could be removed from the fecal stream, even more serious

microorganisms might colonize the gut and affect the anorectal area.

Two clinical trials were reported with a compound containing *E. coli* vaccines (Ref. 1). In the first, 24 patients were treated with an ointment and 28 with a placebo that consisted only of the vehicle (Ref. 1). This report of a trial carried out in Japan noted that the best results were secured with patients with "hemorrodial knots" or "tears in anus." These entities probably should be interpreted as thrombosed hemorrhoids or anal fissures. A second trial was carried out in 40 patients (Ref. 1). In both reports a slight advantage was shown in overall improvement from the use of the vaccines compared with the vehicle itself. However, whether or not the control vehicle contained all substances except *E. coli* breakdown products is not clear.

There are other questions about the effectiveness of *E. coli* vaccines used in these investigations. There is no description of the method by which the organisms are killed; this undoubtedly would affect antigenicity. The preservatives in the combination used may not only influence antibacterial activity but also antigenicity. Metabolic and corpuscular elements, the breakdown products of *E. coli*, in the vaccines are not specified. The strains of *E. coli* are not specified, nor is there any indication as to whether or not the vaccine contains a K antigen. it is stated that the product has not been changed since 1922; this may mean a stock culture has been used, but this is not clear in the data (Ref. 1).

In conclusion, there are no studies available to show the relationship of infection to hemorrhodial symptoms that are amenable to treatment with ingredients approved by this Panel. Nor are there any studies to show that *E. coli* vacine can reduce irritation or pruritis by virtue of its purported immunologic effect. There is some evidence that ingestion or local application of *E. coli* vaccines can induce serum antibodies to *E. coli*, though it is not certain that this applies to other gram-negative bacteria such as *Salmonella*. There is no proof that this increase could be of any substantial quantitative effect insofar as destruction of *E. coli* in the body is concerned. Furthermore, there is the possibility that vaccines, if effective, might indeed be harmful because of other bacteria that would colonize the feces and affect the anorectal area. The data submitted from clinical trials are not adequate to establish general recognition of its effectiveness.

The Panel recognizes some of the claims associated with this ingredient as being effects that are useful in the treatment of anorectal symptoms for relief of irritation and/or pruritus, but believes that immunotherapy, the mechanism by which the claim for relief of infection is inferred, is such a complex process that any preparation claiming effectiveness on such a basis requires further testing before being included in OTC drug products.

A preparation presented to the Panel listed the active ingredients contained in a 1 g suppository as follows: Sterilized conserved metabolites and the corpuscular components of approximately 300 million coli-bacterials of different types (Ref. 1). The following were listed but are considered by the Panel as pharmaceutical aids: Liquefied phenol, neutral oil, adeps solidus, and cialit. Cialit is the sodium salt of 2-(ethylmercurithio)-5-benzoxazol-carboxylic acid. One g of ointment contains sterilized, conserved metabolites and the corpuscular components of approximately 330,000,000 coli-bacterials. The following were listed but are considered by the Panel as pharmaceutical aids: Petrolatum, hydrated lanolin, and amphocerin E (dehydag). No data concerning the safety or effectiveness of cialit or amphocerin E have been submitted. It is impossible from the material presented to separate the effectiveness of *E. coli* vaccines from other components in the combination. While it is considered that these agents act as preservatives or as vehicles and as such are outside the charge of the Panel, the Panel recommends that further information to be reviewed by another Panel is necessary concerning their composition and action.

(4) *Evaluation.* The Panel concludes that the safety and effectiveness of *E. coli* vaccines to relieve irritation, prevent infection, or relieve pruritus in the anorectal area are unproven. In view of the hazards that could result from unbalancing the bacterial flora of the anorectal area, *E. coli* vaccines are not safe and effective for use in anorectal preparations.

References

(1) OTC Volume 120030.

(2) Minutes of the OTC Panel on Hemorrhoidal Drug Products, 16th meeting, September 8 and 9, 1975.

(3) Ewing, W. H., "Enterobacteriaceae Infections," *in* "Diagnostic Procedures for Bacterial, Mycotic and Parasitic Infections," 5th Ed., Edited by Bodily, H. and E. Updike, American Public Health Association, Inc., New York, pp. 227–280, 1970.

(4) Schneerson, R. and J. B. Robbins, "Induction of Serum Haemophilus Influenzae Type B Capsular Antibodies in Adult Volunteers Fed Cross-Reacting Escherichia Coli 075:K100:H5," *New England Journal of Medicine*, 292:1083–1096, 1975.

c. Lappa extract (external and intrarectal use). The Panel concludes that there are no data to establish either the safety or effectiveness of lappa extract in OTC anorectal preparations.

(1) *Description.* Lappa consists of the dried root of *Arctium lappa*. It contains a volatile oil, a bitter principle, inulin, and tannin (Refs. 1 and 2).

The roots of *Arctium lappa* or of *A. minus* were recognized in several editions of standard pharmaceutical references (Refs. 1 and 2). The fluidextract was the preparation of choice. A proprietary product, burdock root oil, was a perfumed mixture of an alcoholic extract of the root with castor oil. These preparations and a poultice prepared from the fresh leaves were used in the treatment of various skin disorders such as psoriasis, prurigo (persistent itching eruptions of papules), and acne. The fluidextract, prepared from the dried root, was prescribed for internal administration in the management of gouty and rheumatic conditions (Ref. 3).

Considerable phytochemical work has been done on the root. Arctium is a reputed narcotic glycoside, but the chemical character of this compound has not been described (Ref. 4). Suchy et al. (Ref. 5) described arctiopicrin, a sesquiterpene lactone, but pharmacological properties have not been described. A substance, arctigenin, is a compound chemically resembling picropodophyllin, but its pharmacological resemblance has not been noted. Arctic acid is a new sulfur-containing acetylenic compound but is without proven pharmacological activity (Ref. 6).

(2) *Safety.* A search of the medical literature of the past 20 years produced no studies on either the safety or effectiveness of lappa. It is essentially a relic of old herbal medicine. One reference states that it was formerly used in the form of a decoction (1 in 20) and as a diuretic and diaphoretic with up to 500 mL being administered daily. The internal dose was given as 1 to 6 g (Ref. 1). Lappa was formerly used for dermatoses (Ref. 2). Claims made for the product published in 1930 were as an aperaitif, diuretic, diaphoretic, and ulcerative (Ref. 7). Externally it was also used for swelling, hemorrhoids, burns, and a hair grower, as an antisyphilitic, antirheumatic, and in large doses as a purgative (Ref. 7). As a purgative, 1 to 6 g of the root has been given with an average dose of 2 g (Ref. 7).

From these reports it would appear that because the oral administration of

lappa has been used in the past, external or intrarectal application would be safe within the limits of practical application, but there are no data to support either the lower or upper limits for this purpose. No reports on the safe application to anorectal disease were found.

(3) *Effectiveness.* From the composition of the root it would suggest that tannins are one of the active ingredients and that these ingredients could act as a mild astringent. An extract of the root has been found to lower blood sugar in rats, but this action has not been verified in other species and it was not quantified in the studies in rats (Ref. 8). Anorectal use of lappa is not currently mentioned in any of the standard pharmacology texts. With the exception of a few testimonials from patients who had used lappa in a combination, no data to support its effectiveness in anorectal disease could be found (Ref. 3).

(4) *Evaluation.* The Panel concludes there are no data to establish a minimum or maximum dose for lappa when contained in anorectal preparations. Safety has not been established, and there is no evidence that could be found to prove its effectiveness in anorectal preparations. This ingredient is therefore placed in Category II.

References

(1) "Martindale. The Extra Pharmacopoeia," 26th Ed., Edited by Blacow, N.W., The Pharmaceutical Press, London, England, p. 2021, 1972.

(2) "The Merck Index," 8th Ed., Merck and Co., Inc., Rahway, NJ, p. 609, 1968.

(3) OTC Volume 120053.

(4) Onaki, T., "Constituents of the Seeds of the Burdock (*Arctium lappa* L.). IV. Racemization of Arctigenin and Its Derivatives," *Journal of the Pharmaceutical Society of Japan,* 57:269–274, 1937.

(5) Suchy, M. et al., "Terpenes. LXXXIV. The Structure of Arctiopicrin, a Sesquiterpene Lactone from *Arctuim minus* Bernh," *Croatica Chemica Acta, 29:247–254, 1957.*

(6) Obata, S., M. Yoshikura and R. Washino, "Components of *Arctium lappa,*" *Nippon Nogei Kagaku Kaishi,* 44:437–446, 1970.

(7) "The Merck Index," 4th Ed., Merck and Co., Inc., Rahway, NJ, p. 293, 1930.

(8) Lapynina, L. A. and T. F. Sysoeva, "Research on Some Plants to Determine Their Sugar-Lowering Properties," *Farmatsevtichnii Zhurnal (Kiev),* 19:52–58, 1964.

d. Leptandra extract (external and intrarectal use). The Panel concludes that leptandra extract is probably safe but there is no proof of its effectiveness in anorectal preparations.

(1) *Description.* Leptandra is formed from the dried rhizome and roots of *L. virginica,* a North American plant. It contains on analysis a starch, esters of cinnamic acid, methaquinones, fatty acids, resins, saponins, tannin, and sugars (Ref. 1). It formerly was recognized in a standard pharmaceutical compendia (Ref. 2).

(2) *Safety.* It probably would be safe in an anorectal preparation because the oral dose of 1 to 4 g of the powder was employed in the past (Ref. 3). However, no safety data for external or intrarectal use have been found.

(3) *Effectiveness.* Leptandra in the form of the powdered dry drug, extract, or freshly gathered drug, was employed in the past as a cathartic in a dosage of 1 to 4 g (Ref. 3). It was believed to also aid as a cholagogue. This action was proved in dogs; an infusion increased total bile output and total cholate production in dogs (Ref. 4). The literature of 1960 to 1975 does not provide other pharmacologic data (Ref. 2).

The use of this ingredient has disappeared from the pharmacologic and pharmaceutic literature. Older texts regard it as a purgative, emetic, cholagogue, alterative, and tonic used for constipation, liver diseases, diarrhea, dysentery, and torpid liver (Ref. 5).

No data are available to indicate that it is effective in anorectal preparations.

(4) *Evaluation.* The Panel concludes that, although leptandra probably is safe for use in anorectal preparations, there is no evidence that it is effective. It is therefore placed in Category II.

References

(1) "The Merck Index," 7th Ed., Merck and Co., Inc., Rahway, NJ, p. 606, 1960.

(2) OTC Voume 120057.

(3) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, Jr., J. B. Lippincott Co., Philadelphia, PA, pp. 1735–1736, 1955.

(4) Petrovskii, G. A. et al, "The Cholagogic Effect of *Bupleurum exaltatum, Agrimonia asiatica, Leontopodium ochroleucum,* and *Veronica virginica,*" *Farmacologiia i Toksikologiia,* 20:75–77, 1957.

(5) "The Merck Index," 4th Ed., Merck and Co., Inc., Rahway, NJ, 1930.

e. *Mullein (external and intrarectal use).* The Panel concludes that mullein is not safe or effective for use in OTC anorectal preparations.

(1) *Description.* Mullein (verbascum, great mullein, mullein dock) is a common weed native to Europe and to the United States. This drug is a carryover from folklore (Ref. 1).

Mullein is considered a demulcent, a soothing, bland substance. Because the Panel has not recognized any beneficial pharmacologic or therapeutic classification of demulcents for use in anorectal disorders, mullein is being considered independently.

(2) *Safety.* No acceptable or satisfactory scientifc data relevant to the safety of mullein for anorectal use was found. Fat droplets from *Verbaseum orientale* were shown to contain an appreciable amount of carotenoids. Severe irritation to tissues where applied is known to occur (Ref. 2).

(3) *Effectiveness.* No evidence that mullein possesses any effectiveness in the treatment of anorectal disorders has been found. Mullein was formerly used in various pectoral complaints and locally applied to inflammation of mucous membranes without rational basis (Ref. 3). Mullein leaves are mucilaginous and are known to contain several saponins but probably in too small quantities to be physiologically important. It is theoretically possible that some therapeutic properties from tannins, flavonoids, or carotenoids (Ref. 4) exist but there are no clinical studies to support any such claim. It is improbable that mullein possesses any significant therapeutic virtues other than that of a demulcent (Ref. 5). Early Californians used mullein externally in pulmonary diseases and sprains. Spanish New Mexicans say that besides being pleasurable, inhaled smoke from cigarettes containing dried mullein leaves is good for asthma, and mullein leaves soaked in "mula blanca" (local corn whiskey) make a beverage that is also beneficial in counteracting the same complaint (Ref. 6).

(4) *Evaluation.* The Panel concludes that there are no data to establish a minimum or maximum dose for mullein applied to anorectal preparations. Nor is there evidence to prove the safety and effectiveness of this ingredient in OTC anorectal products. Therefore, mullein is placed in Category II.

References

(1) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, Jr., J. B. Lippincott, Co., Philadelphia, PA, pp. 1927–1928, 1955.

(2) Groger, D. and P. Simchen, "Zur Kenntnes Iridoider Pflanzenstoffe," *Die Pharmazie,* 22:315–321, 1967.

(3) Parker, K. D., "Rapid Gas Chromatographic Method for Screening of Toxicological Extracts from Alkaloids," *Annals of Chemistry,* 53:356, 1963.

(4) Pastowowy, A., *Acta Polon Pharmacology,* 2:287, 1938.

(5) Archiv Pharmacy, Verlog Chemie, W. Germany, 275, p. 145, 1937.

(6) Curtain, L. S. M., "Herbs of the Upper Rio Grande," Southwest Museum, Los Angeles, CA, p. 166, 1976.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of anorectal drug products are unsupported by scientific data and in some instances by sound theoretical reasoning.

The Panel considers the following claims to be misleading and unsupported by scientific data.

a. "Promotes healing."

b. "Astringent."

c. "Reduces swelling."

d. "An astringent to help reduce swollen tissues."

e. "For a mild local astringent, cooling, soothing and hygienic effect."

f. "Relief without the use of narcotics or astringents of any kind."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.*

None.

The agency has carefully considered the potential environmental impacts of this proposal and has concluded that the action will not have a significant effect on the human environment and that an environmental impact statement therefore will not be prepared. The agency's finding of no significant impact and the evidence supporting this finding contained in an environmental assessment (pursuant to 21 CFR 25.31, proposed December 11, 1979, 44 FR 71742) may be seen in the Office of the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 346, to read as follows:

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

Subpart A—General Provisions

Sec.
346.1 Scope.
346.3 Definitions.

Subpart B—Active Ingredients

346.10 Local anesthetic active ingredients.
346.12 Vasconstrictor active ingredients.
346.14 Protectant active ingredients.
346.16 Counterirritant active ingredients.
346.18 Astringent active ingredients.
346.20 Keratolytic active ingredients.
Sec.
346.22 Permitted combinations of active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

346.50 General labeling of anorectal drug products.
346.52 Labeling of local anesthetic drug products.
346.54 Labeling of vasoconstrictor drug products.
346.56 Labeling of protectant drug products.
346.58 Labeling of counterirritant drug products.
346.60 Labeling of astringent drug products.
346.62 Labeling of keratolytic drug products.

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 346.1 Scope.

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 of the conditions in this Part 346 in addition to each of the general conditions established in § 330.1 of this chapter.

§ 346.3 Definitions.

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

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

(c) *Vasoconstrictor drug.* An agent that causes temporary constriction of blood vessels.

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

(e) *Counterirritant drug.* An agent that produces a local sensation that distracts from the perception of pain, buring, or itching.

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

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

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

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

Subpart B—Active Ingredients

§ 346.10 Local anesthetic active ingredients.

The active ingredients of the product consist of the following when used within the dosage limits established for each ingredient:

(a) Benzocaine 5 to 20 percent in polyethylene glycol ointment.

(b) Pramoxine hydrochloride 1 percent in a cream or jelly formulation.

(1) *For cream formulation.* Pramoxine hydrochloride 1 percent in a cream base containing methylparaben USP, propylparaben USP, cetyl alcohol NF, synthetic spermaceti NF, sodium lauryl sulfate USP, glycerin USP, and purified water USP.

(2) *For jelly formulation.* Pramoxine hydrochloride 1 percent in a jelly base containing propylene glycol USP, hydroxypropyl methylcellulose USP (4000 centipoises), and purified water USP.

§ 346.12 Vasoconstrictor active ingredients.

The active ingredients of the product consist of the following when used within the dosage limits established for each ingredient:

(a) Ephedrine sulfate 2 to 25 milligrams in aqueous solution per dosage unit.

(b) Epinephrine hydrochloride 100 to 200 micrograms in aqueous solution per dosage unit.

(c) Phenylephrine hydrochloride 0.5 milligram in aqueous solution per dosage unit.

§ 346.14 Protectant active ingredients.

The Active ingredients of the product consist of the following when used within the dosage limits established for each ingredient:

(a) Aluminum hydroxide gel 50 percent or greater per dosage unit.

(b) Calamine 5 to 25 percent (based on the zinc oxide content of calamine per dosage unit.

(c) Cocoa butter 50 percent or greater per dosage unit.

(d) Cod liver oil 50 percent or greater per dosage unit.

(e) Gylcerin 50 percent or greater of a 20 to 45 percent solution of glycerin in water per dosage unit.

(f) Kaolin 50 percent or greater per dosage unit.

(g) Lanolin 50 percent or greater per dosage unit.

(h) Mineral oil USP 50 percent or greater per dosage unit.

(i) Shark liver oil 50 percent or greater per dosage unit.

(j) Starch 50 percent or greater per dosage unit.

(k) White petrolatum USP 50 percent or greater per dosage unit.

(l) Wool alcohols 4 to 7 percent per dosage unit.

(m) Zinc oxide 5 to 25 percent per dosage unit.

§ 346.16 Counterirritant active ingredients.

The active ingredient of the product consists of the following when used within the dosage limits established for each ingredient:

(a) Menthol 0.25 to 1.0 percent in aqueous solution.

§ 346.18 Astringent active ingredients.

The active ingredients of the product consist of the following when used within the dosage limit established for each ingredient:

(a) Calamine 5 to 25 percent (based on the zinc oxide content of calamine percent dosage unit.

(b) Witch hazel water 10 to 50 percent per dosage unit.

(c) Zinc oxide 5 to 25 percent per dosage unit.

§ 346.20 Keratolytic active ingredients.

The active ingredients of the product consist of the following when used within the dosage limit established for each ingredient:

(a) Alcloxa 0.2 to 2.0 percent per dosage unit.

(b) Resorcinol 1 to 3 per dosage unit.

§ 346.22 Permitted combinations of active ingredients.

Two but not more than four protectant ingredients identified in § 346.14 may be combined.

Subpart C—[Reserved]

Subpart D—Labeling

§ 346.50 General labeling of anorectal drug products.

The following labeling is applicable as general labeling for anorectal products as well as labeling for specific anorectal ingredients identified in §§ 346.52, 346.54, 346.56, 346.58, 346.60, and 346.62:

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "anorectal agent" or "anorectal product."

(b) *Indications.* The general labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases:

(1) "For the temporary relief of discomfort of (when the product is intended for use on concurrent symptoms, the symptoms must be specified) associated with hemorrhoids and other anorectal disorders."

(2) "For the temporary relief of the discomfort associated with hemorrhoids and other anorectal disorders."

(3) "For the temporary relief of itching associated with hemorrhoids and other anorectal disorders."

(4) "For the temporary relief of anorectal itching."

(5) "For the temporary relief of local itching associated with inflamed hemorrhoidal tissues."

(6) "For the temporary relief from the itching and discomfort associated with hemorrhoids and other anorectal disorders."

(7) "For the temporary relief of the discomforts associated with piles (hormorrhoids) and other anorectal disorders."

(8) "For the temporary relief of symptoms of anorectal disorders."

(9) "Gives temporary relief of anorectal itching."

(10) "Temporary relief of itching discomfort associated with hemorrhoids and other anorectal disorders."

(11) "For the temporary relief of symptoms associated with hemorrhoids and other anorectal disorders."

(12) "To temporarily soothe local discomfort associated with hemorrhoids and other anorectal disorders."

(13) "To help relieve the discomfort associated with hemorrhoids and other anorectal disorders."

(14) "For the temporary relief of itching."

(15) "For the temporary relief of symptoms of inflammation associated with hemorrhoidal tissues."

(16) "Gives temporary relief of discomfort due to external hemorrhoids and other anorectal disorders."

(17) "For the temporary relief of pruritus ani."

(c) *Warnings.* Warning statements may be combined to eliminate the duplication of words or phrases, but the combined warning statement must be clear and understandable with no decrease in meaning and emphasis. Warning statements must be included on the immediate product container and the package in a 'box border'; they should be printed in black ink or in the color of the most prominent type appearing on either the container or the package, that is, in such a fashion that the prominence and meaning of the warning is not obscured. Appropriate use of printing techniques, styles, colors, and illustration should be utilized to aid the consumer in encountering and understanding the important meaning of the labeling. Warning or caution statements should be typeset in no less than eight-point type, or one-third the point size of the largest type face appearing on both the container and labeling, whichever is larger. The general labeling of the product contains the following general warnings under the heading "Warnings";

(1) "If symptoms do not improve, do not use this product for more than 7 days and consult a physician."

(2) "Do not exceed the recommended daily dosage except under the advice and supervision of a physician."

(3) "If itching persists for more than 7 days, consult a physician."

(4) "In case of bleeding, consult a physician promptly."

(5) *For anorectal products containing perfume.* "If redness, burning, itching, swelling, pain, or other symptoms develop or increase, discontinue use and consult a physician."

(6) *For products for external use—For products that are ointments, creams, jellies, foams, pads, or gels for external use only.* "Do not put this product into the rectum by using fingers or any mechanical device or applicator."

(7) *For products for intrarectal use—*

(i) *For all anorectal products for intrarectal use by insertion into the rectum, except ingredients identified in § 346.14.* "The safety of this product has not been established for use by pregnant women or by nursing mothers."

(ii) *For products that are to be used with special applicators such as pile pipes or other mechanical device.* "Do not use this product if the introduction into the rectum causes additional pain. Consult a physician promptly."

(iii) *For anorectal products that contain at least one anorectal ingredient identified in §§ 346.10, 346.12, 346.16, or 346.20 other than a protectant or astringent anorectal ingredient identified in §§ 346.14 and 346.18.* "Do not use this product in children under 12 years of age except under the advice and supervision of a physician."

(d) *Directions.* Many anorectal products may be used externally as well as intrarectally. Whenever a product is for both external and intrarectal use, the labeling of the product contains a clear separation of each set of directions under the headings, "For external use" and "For intrarectal use." The general labeling of the product contains the following statements or information under the required heading "Directions," followed by "or as directed by a physician."

(1) *For all products.* Recommended or usual dosage, frequency of

(4) "Temporarily protects irritated areas from irritating materials."

(5) "Temporarily relieves anorectal itching."

(6) "Temporarily relieves burning."

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

(8) "For the temporary relief of itching associated with hemorrhoids, inflamed hemorrhoidal tissue or other anorectal disorders."

(9) "For the temporary relief of local itching associated with hemorrhoids, inflamed hemorrhoidal tissues, or other anorectal disorders."

(10) "For the temporary relief from the itching and discomfort due to hemorrhoids or other anorectal disorders."

(11) "Temporarily provides a bland, soothing coating for relief of anorectal discomforts."

(12) "Temporarily provides lubrication in the anorectal area."

(13) "Temporarily lubricates and protects the inflamed irritated anorectal surface to help make bowel movements less painful."

(14) "Temporarily protects from irritation and abrasion during bowel movement."

(15) "Temporarily helps soften and lubricate dry inflamed perianal skin."

(16) "Temporarily relieves the symptoms of perianal skin irritation, and itching."

(17) "Provides lubrication and may help make bowel movements more comfortable."

(18) *For products containing alumina gel identified in § 346.14(a) and for products containing kaolin identified in § 346.14(f).* (i) "For the temporary relief of itching associated with moist anorectal conditions."

(ii) "Temporarily protects irritated areas from irritating materials."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing alumina gel identified in § 346.14(a) and for products containing kaolin identified in § 346.14(f).* "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."

(2) *For products containing wool alcohols identified in § 346.14(l) when wool alcohols have been added to the final formulation as separate ingredient.* "*Caution:* Certain persons can develop allergic reactions to ingredients in this product. If redness, irritation, swelling, pain or other symptoms develop or increase, discontinue use and consult a physician."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as directed by a physician."

(1) *For products containing alumina gel identified in § 346.14(a).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(2) *For products containing calamine identified in § 346.14(b).* Adult external and intrarectal dosage is 5 to 25 percent per dosage unit (based on the zinc oxide content of calamine) and not to exceed six applications per 24 hours or after each bowel movement.

(3) *For products containing cocoa butter identified in § 346.14(c).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(4) *For products containing cod liver oil identified in § 346.14(d).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement and not to exceed 10,000 International Units vitamin A and 400 International Units vitamin D per 24 hours.

(5) *For products containing glycerin identified in § 346.14(e).* Adult external dosage is 20 to 45 percent glycerin in aqueous solution when used in concentrations of at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(6) *For products containing kaolin identified in § 346.14(f).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(7) *For products containing lanolin identified in § 346.14(g).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(8) *For products containing mineral oil identified in § 346.14(h).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(9) *For products containing shark liver oil identified in § 346.14(i).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement and not to exceed 10,000 International Units vitamin A and 400 International Units vitamin D per 24 hours.

(10) *For products containing starch identified in § 346.14(j).* Adult external and intrarectal dosage at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(11) *For products containing white petrolatum identified in § 346.14(k).* Adult external and intrarectal dosage is at least 50 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(12) *For products containing wool alcohols identified in § 346.14(l).* Adult external and intrarectal dosage is 4 to 7 percent per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(13) *For products containing zinc oxide identified in § 346.14(m).* Adult external and intrarectal dosage is 5 to 25 percent dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

§ 346.58 Labeling of counterirritant drug products.

The labeling of the product contains the following information as well as any applicable general labeling identified in § 346.50:

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "anorectal agent" or as an "anorectal product."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases for any ingredient identified in § 346.16:

(1) *For all products.* (i) "For the temporary relief of itching or pain in the perianal area."

(ii) "Can help distract from pain or itch."

(iii) "Temporary relief of itch or pain in the perianal area."

(2) *For products containing menthol identified in § 346.16.* (i) "May provide a cooling sensation."

(ii) "Temporarily relieves itching and soothes burning."

(c) *Warning.* The labeling of the products contains the following warning under the heading "Warning": *For products containing menthol identified in § 346.16. "Caution:* Certain persons can develop allergic reactions to ingredients in this product. If redness, irritation, swelling, pain or other symptoms develop or increase, discontinue use and consult a physician."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as

directed by a physician." *For products containing menthol identified in § 346.16.* Adult external dosage is 0.25 to 2.0 percent per dosage unit in aqueous solution and not to exceed six applications per 24 hours.

§ 346.60 Labeling of astringent drug products.

The labeling of the product contains the following information as well as any applicable general labeling identified in § 346.50:

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "anorectal agent" or as an "anorectal product."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to one or more of the following phrases for any ingredient identified in § 346.18:

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

(2) "Temporary relief of irritation."

(3) "Temporary relief of itching."

(4) "Temporary relief of burning."

(5) "Temporarily relieves itching and soothes burning."

(6) "Temporarily relieves discomfort."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings": General warnings under § 346.50(c) apply.

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as directed by a physician."

(1) *For products containing calamine identified in § 346.18(a).* Adult external and intrarectal dosage in 5 to 25 percent calamine per dosage unit (based on the zinc oxide content of calamine) and not to exceed 6 applications per 24 hours or after each bowel movement.

(2) *For products containing witch hazel water identified in § 346.18(b).* Adult external dosage in 10 to 50 percent witch hazel water per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

(3) *For product containing zinc oxide identified in § 346.18(c).* Adult external and intrarectal dosage is 5 to 25 percent zinc oxide per dosage unit and not to exceed six applications per 24 hours or after each bowel movement.

§ 346.62 Labeling of keratolytic drug products.

The labeling of the product contains the following information as well as any applicable general labeling identified in § 346.50:

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "anorectal agent" or as an "anorectal product."

(b) *Indications.* The labeling of the product contains the following statement of the indications under the heading "Indications" that is limited to the following phrase for any ingredient identified in § 346.20: "For the temporary relief of itching."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing resorcinol identified in § 346.20(b).*

(i) *"Caution:* Certain persons can develop allergic reactions to ingredients in this product. If redness, irritation, swelling, pain, or other symptoms develop or increase, discontinue use and consult a physician."

(ii) "Do not use in open wounds near the anus."

(2) [Reserved]

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions," followed by "or as directed by a physician."

(1) *For products containing alcloxa identified in § 346.20(a).* Adult external dosage is 0.2 to 2.0 percent per dosage unit and not to exceed six applications per 24 hours.

(2) *For products containing resorcinol identified in § 346.20(b).* Adult external dosage is 1 to 3 percent per dosage unit and not to exceed six applications per 24 hours.

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before August 18, 1980. Such comments should be addressed to the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a memorandum or brief. Comments replying to comments may also be submitted on or before September 24, 1980. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: May 13, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80–15334 Filed 5–23–80; 8:45 am]

BILLING CODE 4110–03–M